

Authors	Author Address	Title	Publication	Abstract
Abbey SE, Garfinkel PE.	Department of Psychiatry, Toronto Hospital, Ont., Canada.	Neurasthenia and chronic fatigue syndrome: the role of culture in the making of a diagnosis.	Am J Psychiatry 1991 Dec;148(12):1638-46 comment in: Am J Psychiatry. 1992 Dec;149(12):1753;	Chronic fatigue syndrome is an increasingly popular diagnosis consisting of multiple psychiatric and somatic symptoms. It bears a striking resemblance to the nineteenth-century diagnosis of neurasthenia. Both disorders arose during periods characterized by a preoccupation with commerce and material success and major changes in the role of women. They illustrate the role of culture in the development of a new diagnosis that emphasizes a "medical" rather than "psychiatric" etiology. The authors argue that chronic fatigue syndrome will meet the same fate as neurasthenia--a decline in social value as it is demonstrated that the majority of its sufferers are experiencing primary psychiatric disorders or psychophysiological reactions and that the disorder is often a culturally sanctioned form of illness behavior.
Abbey SE, Garfinkel PE.	Department of Psychiatry, Toronto Hospital, Ontario, Canada.	Chronic fatigue syndrome and depression: cause, effect, or covariate.	Rev Infect Dis 1991 Jan- Feb;13 Suppl 1:S73-83	Depressed mood and the psychiatric diagnosis of major depressive episode (MDE) are common findings in patients with chronic fatigue syndrome (CFS). The relationship between depression and CFS is unclear and may be explained by one of four models: (1) CFS is an atypical manifestation of MDE; (2) depression is the result of CFS as either an organic mood syndrome or an adjustment reaction; (3) CFS and MDE are covariates; and (4) the diagnosis of MDE is artifactual. The evidence for these models is discussed. The potentially confounding effect of depression on tests of immune function and neuropsychological testing is described. The implications of these different models for the design of studies of CFS are examined.
Ablashi DV, Balachandran N, Josephs SF, Hung CL, Krueger GR, Kramarsky B, Salahuddin SZ, Gallo RC.	Laboratory of Cellular and Molecular Biology, National Cancer Institute, Bethesda, Maryland 20892.	Genomic polymorphism, growth properties, and immunologic variations in human herpesvirus-6 isolates.	Virology 1991 Oct;184(2):545-52	Fifteen human herpesvirus-6 (HHV-6) isolates from normal donors and patients with AIDS, systemic lupus erythematosus, chronic fatigue syndrome, collagen-vascular disease, leukopenia, bone marrow transplants, Exanthem subitum (roseola), and atypical polyclonal lymphoproliferation were studied for their tropism to fresh human cord blood mononuclear cells, growth in continuous T cell lines, reactivity to monoclonal antibodies, and by restriction enzyme banding patterns. All isolates replicated efficiently in human cord blood mononuclear cells, but mitogen stimulation of the cells prior to infection was required. The ability to infect continuous T-cell lines varied with the isolates. Isolates similar to GS prototype infected HSB2 and Sup T1 cells and did not infect Molt-3 cells, whereas isolates similar to Z-29 infected Molt-3 cells but not HSB2 and Sup T1 cells. Some of the monoclonal antibodies directed against the HHV-6 (GS) isolate showed reactivity with all isolates tested, but others only reacted with HHV-6 isolates similar to the GS isolate and not with those similar to Z-29 isolate. Restriction enzyme analysis using EcoRI, BamHI, and HindIII revealed that HHV-6 isolates from roseola, bone marrow transplant, leukopenia, and an HIV-1-positive AIDS patient from Zaire (Z-29) were closely related but distinct from GS type HHV-6 isolates. Based on the above findings, we propose that, like herpes simplex virus types 1 and 2, the 15 HHV-6 isolates analyzed can be divided into group A (GS type) and group B (Z-29 type).
Ablashi DV, Salahuddin SZ, Josephs SF, Balachandran N, Krueger GR, Gallo RC.	National Cancer Institute, NIH, Bethesda, MD 20892.	Human herpesvirus-6 (HHV- 6) (short review).	In Vivo 1991 May- Jun;5(3):193-9	Human Herpesvirus-6 is the etiological agent of Roseola infantum and approximately 12% of heterophile antibody negative infectious mononucleosis. HHV-6 is T-lymphotropic, and readily infects and lyses CD4+ cells. The prevalence rate of HHV-6 in the general population is about 80% (as measured by IFA) with an IgG antibody titer of 1:80. A lower prevalence, however, is observed in some countries. HHV-6 is reactivated in various malignant and non-malignant diseases as well as in Chronic Fatigue Syndrome and transplant patients. Furthermore, elevated antibody titers were also observed in lymphoproliferative disorders, auto-immune diseases and HIV-1 positive AIDS patients. There appears to be some strain variability in HHV-6 isolates. The GS isolates of HHV-6 (prototype) was resistant to Acyclovir, Gancyclovir, but its replication was inhibited by Phosphonoacetic acid and Phosphoformic acid. HHV-7 isolated from healthy individuals showed, by restriction analysis, that 6 out of 11 probes derived from two strains of HHV-6, cross-hybridized with DNA fragments, derived from HHV-7.
Ablashi DV, Zompetta C, Lease C, Josephs SF, Balachandra N, Komaroff AL, Krueger GR, Henry B, Lukau J, Salahuddin SZ.		Human herpesvirus 6 (HHV6) and chronic fatigue syndrome (CFS).	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:33-40	

Alisky JM, Iczkowski KA, Foti AA.	Chronic fatigue syndrome.		Am Fam Physician 1991 Jul;44(1):56, 61. Erratum in: Am Fam Physician 1991 Aug;44(2):406	
Anon		[Chronic fatigue syndrome].[article in Dutch]	Ned Tijdschr Geneesk 1991 Dec 7;135(49):2347-9 comment on: Ned Tijdschr Geneesk. 1991 Oct 26;135(43):2005-9	
Anon		Alleged link between hepatitis B vaccine and chronic fatigue syndrome.	Can Dis Wkly Rep 1991 Oct 5;17(40):215-6	
Anon		Magnesium and chronic fatigue syndrome.	Lancet 1991 May 25;337(8752):1295	
Anon		Magnesium and chronic fatigue syndrome.	Lancet 1991 May 4;337(8749):1094-5 comment on: Lancet. 1991 Mar 30;337(8744):757-60	
Anon		Chronic fatigue syndrome-- false avenues and dead ends.	Lancet 1991 Feb 9;337(8737):331-2	
Anon		Chronic fatigue syndrome definition sparks off debate.	Nurs Times 1991 Jan 16-22;87(3):13 comment on: Nurs Times. 1990 Nov 21-27;86(47):40-3	
Anon		Chronic fatigue syndrome.	JAMA 1991 Jan 16;265(3):357-8 comment on: JAMA. 1990 Jul 4;264(1):48-53	
Anon		Chronic Fatigue Syndrome. Proceedings of a workshop. Toronto, Ontario, 28-29 September 1989. Overall	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:1-71	
Anon		Considerations in the design of studies of chronic fatigue syndrome. Pittsburgh, Pennsylvania, 15-16 September 1988. Overall	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S1-140	
Armon C, Kurland LT.	Department of Neurology, Mayo Clinic, Rochester, Minnesota 55905.	Chronic fatigue syndrome: issues in the diagnosis and estimation of incidence.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S68-72	This article critiques the current working definition of chronic fatigue syndrome. The concerns raised about the current working definition are the following: prolonged or excessive exertion is not addressed explicitly; duration and quality of bed rest are not specified; a socioeconomic ascertainment bias is present; data from history and physical findings are not clearly separated and are relegated to minor criteria; and the rigor of neurologic and psychiatric evaluations is not specified. We propose a flow chart that addresses the possible modes of evolution of chronic fatigue syndrome for patients; this chart may yield more homogeneous subgroups of individuals with this syndrome or enable some patients to avert the syndrome.
Arnason BG.	Department of Neurology, University of Chicago, Illinois 60637.	Nervous system-immune system communication.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S134-7	This essay is based on the premise that certain individuals may have a biologically determined propensity to respond to infection that is manifested by the development of disease such as chronic fatigue syndrome; the sequence of events that leads to this response involves the immune system. Biochemical pathways between the immune and nervous systems are reviewed, and the role of various products in the systemic circulation, including interleukin-1, pituitary hormone, and catecholamines, is highlighted. This premise could be tested by measuring levels of these substances in carefully selected

				patients and controls.
Arya DK.		Chronic fatigue syndrome.	Br J Gen Pract 1991 Nov;41(352):480 comment on: Br J Gen Pract. 1991 Aug;41(349):324-6 Br J Gen Pract. 1991 Aug;41(349):339-42	
Balachandran N, Tirawatnapong S, Pfeiffer B, Ablashi DV, Salahuddin SZ.	Department of Microbiology, Molecular Genetics, and Immunology, University of Kansas Medical Center, Kansas City 66103.	Electrophoretic analysis of human herpesvirus 6 polypeptides immunoprecipitated from infected cells with human sera.	J Infect Dis 1991 Jan;163(1):29-34	Proteins of human herpesvirus 6 (HHV-6) eliciting human antibody responses were examined in serum from healthy adults and patients with AIDS, chronic fatigue syndrome, Hodgkin's disease, and Sjogren's syndrome. HHV-6 IgG antibody titers measured by immunofluorescence (IF) ranged from 1:10 to 1:1280. Lysates of HHV-6-infected and uninfected cells labeled with [35S]methionine, [3H]glucosamine, and 125I were immunoprecipitated with sera and analyzed electrophoretically. Sera with IF titers greater than or equal to 1:20 immunoprecipitated greater than 20 [35S]methionine-labeled HHV-6 polypeptides of approximately 26-180 kDa. At least 10 HHV-6 glycoproteins and 8 HHV-6 polypeptides associated with the surfaces of infected cells were recognized by human sera. The approximate molecular masses of glycoproteins immunoprecipitated by human sera were similar to those immunoprecipitated by monoclonal antibodies. The labeling intensity of HHV-6 protein bands increased with increasing IF titer, and the effect was most prominent for HHV-6 glycopolypeptides. No reactivities with specific HHV-6 polypeptide(s) were characteristic of a given patient group. These findings suggest that HHV-6 glycoproteins are good targets for human antibody responses.
Barofsky I, Legro MW.	Institute of Social Oncology, Silver Spring, Maryland.	Definition and measurement of fatigue.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S94-7	Although fatigue is a key component of the chronic fatigue syndrome, its definition and measurement remain relatively undeveloped. Most research on fatigue has been oriented towards work or performance of tasks and has involved laboratory studies of healthy individuals, while the study of fatigue as encountered in clinical settings has received minimal attention from investigators. This paper recommends that the natural history of chronic fatigue in its various clinical presentations be studied and that standardized assessment tools be used in this process. An investigation of the tools available for the assessment of fatigue yielded single-item, unidimensional, and multidimensional instruments. Additionally, the apparent association between affective illness and the chronic fatigue syndrome is addressed, and the fact that this relationship depends on issues of measurement is explored.
Becker JT.	Department of Psychiatry, University of Pittsburgh School of Medicine, Pennsylvania.	Methodologic considerations in assessment of cognitive function in chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S112-3	Rigorous and standardized assessment of cognitive function is an important component of any multidisciplinary study of chronic fatigue syndrome. The present paper describes some methodologic issues that need to be addressed to maximize the yield from any neuropsychiatric evaluation of the syndrome.
Bell KM, Cookfair D, Bell DS, Reese P, Cooper L.	Monroe County Health Department, Rochester, New York 14692.	Risk factors associated with chronic fatigue syndrome in a cluster of pediatric cases.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S32-8	After seven pediatric cases of chronic fatigue syndrome (CFS) were diagnosed in a farming community in upstate New York, a questionnaire regarding symptoms and potential risk factors of CFS was distributed to all students enrolled in the same school district. Twenty-one students with symptoms of CFS were identified. Two controls per case matched for age and sex were randomly selected from questionnaire respondents. Health status was verified for all subjects by telephone, and diagnosis of CFS was confirmed by a physician. Information was collected on the following factors: symptoms of CFS among other family members; history of allergy/asthma; consumption of raw milk, raw eggs, raw cheese, or raw meat; water supply; exposure to animals; home heating source; proximity to farmland/orchards; tick bite; blood transfusion; camping; and appendicitis. Logistic-regression analyses indicated that the best model (characterized by symptoms among other family members, recent ingestion of raw milk, and history of allergy/asthma) produced significant estimates of relative risk (P less than .05) of 35.9, 44.3, and 23.3, respectively, for the three factors (corrections were made for the effect of the other covariates). These data suggest that a combination of host and environmental factors, including an infectious agent or agents, are involved in the etiology of CFS.
Bertram G, Dreiner N, Krueger GR, Ramon A, Ablashi DV, Salahuddin SZ, Balachandram N.	ENT Clinic Dortmund, University Witten-Herdecke, F.R.G.	Frequent double infection with Epstein-Barr virus and human herpesvirus-6 in patients with acute infectious	1492: In Vivo 1991 May-Jun;5(3):271-9	Clinical infectious mononucleosis (IM) represents a benign self-limited form of lymphoproliferative disease which is usually caused by infection with Epstein-Barr virus (EBV). Microscopic characteristics of this lymphoproliferative disorder, however, are not ultimately specific for EBV infection, but can also be seen in infections with other lymphotropic viruses, especially of the

		mononucleosis.		herpesvirus family. Human herpesvirus-6 (HHV-6) infection can apparently be associated with a number of diseases also seen in EBV infection. Also, postinfectious chronic fatigue syndrome (PICFS) which may follow IM is in more than 60% of the cases accompanied by persistent active HHV-6 infection. We thus screened serologically 215 cases of acute IM for evidence for infection with EBV, HHV-6 and CMV. Patients were tentatively grouped into those having primary infection or reactivated (probably non-primary) infections. Cases were followed for two years to monitor changes in titers. Of all 215 cases, 211 (98.1%) were positive for EBV, 137 (63.7%) for primary infections, 21 (9.8%) for reactivated infection, and 53 (24.6%) for latent EBV. Thirty-three (15.3%) cases had primary HHV-6 infection, 63 (29.3%) active or reactivated HHV-6 infection, and 71 (33.9%) latent HHV-6. Double active EBV and HHV-6 infection, including primary and reactivated infections, amounted to 89 (39.5%) cases. Cytomegalovirus (CMV) antibody titers were found in 81 (37%) cases, 48 (22.3%) of which indicated latent infection and 33 (15.3%) active infection. Only two cases had evidence of active CMV infection alone, 1 cases of active CMV and HHV-6 infection. Serologic titers in 12 (5.6%) cases indicated combined active infection with CMV, EBV and HHV-6.(ABSTRACT TRUNCATED AT 250 WORDS)
Blakely AA, Howard RC, Sosich RM, Murdoch JC, Menkes DB, Spears GF.	Department of Psychological Medicine, Otago Medical School, University of Otago, Dunedin, New Zealand.	Psychiatric symptoms, personality and ways of coping in chronic fatigue syndrome.	Psychol Med 1991 May;21(2):347-62	This study aimed to investigate the psychological characteristics of chronic fatigue syndrome (CFS: Holmes et al. 1988). A battery of psychometric instruments comprising the General Health Questionnaire (GHQ), the Beck Depression Inventory (BDI), the Minnesota Multiphasic Personality Inventory (MMPI) and the Lazarus Ways of Coping (WoC) inventory, was administered to a sample of clinically-defined CFS sufferers (N = 58), to a comparison group of chronic pain (CP) patients (N = 81) and to a group of healthy controls matched for sex and age with the CFS sample (N = 104). Considerable overlap was found between CFS and CP patients at the level of both physical and psychological symptoms. This raises the possibility that CFS sufferers are a sub-population of CP patients. However, while there was some commonality between CFS and CP patients in terms of personality traits, particularly the MMPI 'neurotic triad' (hypochondriasis, depression and hysteria), CFS patients showed more deviant personality traits reflecting raised levels on the first MMPI factor, emotionality. Moreover, results were not consistent with the raised emotionality being a reaction to the illness, but rather were consistent with the hypothesis that emotionality is a predisposing factor for CFS. The majority of CFS patients fell within four personality types, each characterized by the two highest MMPI scale scores. One type (N = 20) reported a lack of psychological symptoms or emotional disturbance contrary to the overall trend for the CFS sample. This group conformed to the ICD-10 classification of neurasthenia.
Brancati FL.		Intravenous immunoglobulin treatment of chronic fatigue syndrome.	Am J Med 1991 Sep;91(3):320-1 comment on: Am J Med. 1990 Nov;89(5):551-3 Am J Med. 1990 Nov;89(5):561-8	
Brodsky CM.	Department of Psychiatry, School of Medicine, University of California, San Francisco.	Depression and chronic fatigue in the workplace. Workers' compensation and occupational issues.	Prim Care 1991 Jun;18(2):381-96	There is ample evidence that some forms of depression can be caused or aggravated by work. The relationship of work and chronic fatigue syndrome is questionable, but elements at work can aggravate the symptoms of chronic fatigue syndrome. The role of physicians who can support or discourage beliefs about physical illness is all important, both by what they say and how they treat. In the process of interaction, they can promote or discourage disability. The role of the physician in the workplace is to determine if an illness is work related, if it is disabling, if it requires treatment, and what treatment. The physician must advise if the worker can continue in his or her usual and customary employment and, if not, if he or she can be vocationally rehabilitated from a medical standpoint. Conditions in which physical symptoms are unsupported by physical findings and have diagnostic labels that describe the disorder without indicating either cause or pathology are especially troubling for the physician who must decide if the patient's job caused the symptoms.
Buchwald D, Komaroff AL.	Department of Medicine, Harborview Medical Center, University of Washington School of Medicine, Seattle.	Review of laboratory findings for patients with chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S12-8	Various abnormalities revealed by laboratory studies have been reported in adults with chronic fatigue syndrome. Those most consistently reported include depressed natural killer cell function and reduced numbers of natural killer cells; low levels of circulating immune complexes; low levels of several autoantibodies, particularly antinuclear antibodies and antithyroid antibodies; altered levels of

				immunoglobulins; abnormalities in number and function of lymphocytes; and modestly elevated levels of two Epstein-Barr virus-related antibodies, immunoglobulin G to viral capsid antigen and to early antigen.
Buchwald D, Wener MH, Komaroff AL.	University of Washington, Seattle, WA.	Anti-neuronal antibody levels in chronic fatigue syndrome patients with neurologic abnormalities.	Arthritis Rheum 1991 Nov;34(11):1485-6	
Butler S, Chalder T, Ron M, Wessely S.	Department of Psychiatry, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.	Cognitive behaviour therapy in chronic fatigue syndrome.	J Neurol Neurosurg Psychiatry 1991 Feb;54(2):153-8	Fifty patients fulfilling operational criteria for the chronic fatigue syndrome (CFS), and who had been ill for a mean of five years, were offered cognitive behaviour therapy in an open trial. Those fulfilling operational criteria for depressive illness were also offered tricyclic antidepressants. The rationale was that a distinction be drawn between factors that precipitate the illness and those that perpetuate it. Among the latter are cognitive factors such as the belief that physical symptoms always imply tissue damage, and behavioural factors such as persistent avoidance of activities associated with an increase in symptoms. Therapy led to substantial improvements in overall disability, fatigue, somatic and psychiatric symptoms. The principal problems encountered were a high refusal rate and difficulties in treating affective disorders. Outcome depended more on the strength of the initial attribution of symptoms to exclusively physical causes, and was not influenced by length of illness. These results suggest that current views on both treatment and prognosis in CFS are unnecessarily pessimistic. It is also suggested that advice currently offered to chronic patients, to avoid physical and mental activity, is counterproductive.
Byrne E.	Neurology Department, St. Vincent's Hospital, Melbourne.	The chronic fatigue syndrome: a reappraisal and unifying hypothesis.	Clin Exp Neurol 1991;28:128-38	The chronic fatigue syndrome is one of the most common medical problems in Western countries. Research work in virology, immunology, metabolic medicine and psychiatry in this area is reviewed and a disease model proposed. The chronic fatigue syndrome can be considered as a continuum ranging from cases with chronic viraemia on the one hand to instances of frank psychiatric illness on the other. In the majority of patients the fully evolved syndrome may involve an interaction of premorbid factors (psychological, immunological), environmental trigger factors (virus) and enhancing factors (emotional response to illness). A Venn diagram is a convenient way of expressing this concept.
Cassel W, Archer-Duste H.		The new epidemic: chronic fatigue syndrome.	Pa Nurse 1991 Feb;46(2):8-9	
Chao CC, Janoff EN, Hu SX, Thomas K, Gallagher M, Tsang M, Peterson PK.	Department of Medicine, Hennepin County Medical Center, Minneapolis, MN 55415.	Altered cytokine release in peripheral blood mononuclear cell cultures from patients with the chronic fatigue syndrome.	Cytokine 1991 Jul;3(4):292-8	Chronic fatigue syndrome (CFS) is an idiopathic illness associated with a variety of immunologic abnormalities. To investigate potential pathogenetic mechanisms, we evaluated serum levels and peripheral blood mononuclear cell (PBMC) production of selected cytokines and immunoglobulins. Serum bioactive transforming growth factor beta (TGF-beta) levels were higher (P less than 0.01) in patients with CFS (290 +/- 46 pg/mL) than in control subjects (104 +/- 18 pg/mL), but levels of other cytokines tested were not different. Lipopolysaccharide-stimulated release of interleukin 1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha was increased (P less than 0.05) in PBMC cultures from patients with CFS versus control subjects; enhanced (P less than 0.01) IL-6 release to phytohemagglutinin was also observed. In contrast, TGF-beta release in response to lipopolysaccharide was depressed (P less than 0.01) in PBMC cultures derived from patients with CFS. No differences in IL-2 and IL-4 or immunoglobulin production were observed. The enhanced release of inflammatory cytokines by stimulated PBMC from patients with CFS suggests that these cells are primed for an increased response to immune stimuli. These data also suggest an association between abnormal regulation of TGF-beta production in vivo and in vitro with the immunologic consequence of CFS.
Cluff LE.	Robert Wood Johnson Foundation, Princeton, New Jersey.	Medical aspects of delayed convalescence.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S138-40	Disease and illness are not synonymous. In most instances, disease is demonstrable by anatomic, physiologic, biochemical, microbiologic, or immunologic abnormalities. Disease is a pathologic process. Not all persons with a disease are sick or ill. Symptoms of illness associated with a disease may be manifest or persist after the disease has disappeared. The absence of demonstrable disease, however, does not necessarily mean that symptoms of illness are unreal. Recovery from disease and recovery from illness are not always equated. Many factors, including personal characteristics and social circumstances, can be responsible for recovery from disease and illness. Chronic fatigue

				syndrome or symptoms of illness can persist in some patients but not in others after many different diseases.
Collignon P.		Immunoglobulin treatment for chronic fatigue syndrome.	Am J Med 1991 Oct;91(4):443-4 comment on: Am J Med. 1990 Nov;89(5):561-8	
Comtois R.	Hopital Notre-Dame, Montreal, Quebec.	[Chronic fatigue: myth or reality]?[article in French]	Union Med Can 1991 Jan-Feb;120(1):10-6	Chronic fatigue is one of the most common complaints. However, it can be a vexing problem in clinical practice. In contrast to serum cholesterol or blood pressure, fatigue may seem immeasurable. The management of fatigue is often complicated by the uncertainty surrounding of its cause and the frequent lack of specific therapy. Recently, criteria were established for the diagnosis of chronic fatigue syndrome. This working case definition does provide some guidance for the practicing physician.
Cooke RG.		The psychiatrist and chronic fatigue syndrome.	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:13-5	
Cotton P.		Treatment proposed for chronic fatigue syndrome; research continues to compile data on disorder.	JAMA 1991 Nov 20;266(19):2667-8	
Covington EC.	Department of Psychiatry, Cleveland Clinic Foundation, Ohio.	Depression and chronic fatigue in the patient with chronic pain.	Prim Care 1991 Jun;18(2):341-58	Chronic benign pain is commonly associated with chronic fatigue and depression. Depression and chronic fatigue syndrome are also associated with each other and often include pain. Psychologic factors are prominent in these conditions, and they may share neurobiologic factors as well. Management requires separately addressing each component of patients' distress and usually includes physical rehabilitation, education, administration of nonhabituating medications and often counseling. Depression may be a favorable prognostic sign, as it suggests a treatable condition and provides incentive for recovery.
Cox IM, Campbell MJ, Dowson D.	Medical School, University of Southampton, UK.	Red blood cell magnesium and chronic fatigue syndrome.	Lancet 1991 Mar 30;337(8744):757-60 comment in: Lancet. 1991 Jul 6;338(8758):66 Lancet. 1991 May 4;337(8749):1094-5 Lancet. 1991 Sep 7;338(8767):641 Lancet. 1992 Jul 11;340(8811):124-5	The hypotheses that patients with chronic fatigue syndrome (CFS) have low red blood cell magnesium and that magnesium treatment would improve the wellbeing of such patients were tested in a case-control study and a randomised, double-blind, placebo-controlled trial, respectively. In the case-control study, 20 patients with CFS had lower red cell magnesium concentrations than did 20 healthy control subjects matched for age, sex, and social class (difference 0.1 mmol/l, 95% confidence interval [CI] 0.05 to 0.15). In the clinical trial, 32 patients with CFS were randomly allocated either to intramuscular magnesium sulphate every week for 6 weeks (15 patients) or to placebo (17). Patients treated with magnesium claimed to have improved energy levels, better emotional state, and less pain, as judged by changes in the Nottingham health profile. 12 of the 15 treated patients said that they had benefited from treatment, and in 7 patients energy score improved from the maximum to the minimum. By contrast, 3 of the 17 patients on placebo said that they felt better (difference 62%, 95% CI 35 to 90), and 1 patient had a better energy score. Red cell magnesium returned to normal in all patients on magnesium but in only 1 patient on placebo. The findings show that magnesium may have a role in CFS. Randomized Controlled Trial
Crowley JP.		Chronic fatigue syndrome.	R I Med J 1991 Jul;74(7):310-1	
Dale JK, Di Bisceglie AM, Hoofnagle JH, Straus SE.	Medical Virology Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892.	Chronic fatigue syndrome: lack of association with hepatitis C virus infection.	J Med Virol 1991 Jun;34(2):119-21	Chronic fatigue syndrome (CFS) is a debilitating heterogeneous disorder lacking consistent, objective physical or laboratory abnormalities. Among the hypothetical etiologies for CFS are chronic viral infections. The present controlled seroprevalence study found that, among typical CFS patients, evidence of hepatitis C virus (HCV) infection is uncommon. Only one of 36 patients and none of 14 controls were anti-HCV positive. The positive patient had persistent aminotransferase elevations and prior posttransfusion hepatitis. Thus HCV infection is not a common feature of CFS and should not be routinely sought.
Daugherty SA, Henry BE, Peterson DL, Swarts RL, Bastien S, Thomas RS.	Department of Family Medicine, University of Nevada School of Medicine,	Chronic fatigue syndrome in northern Nevada.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S39-44	The clinical and laboratory findings from studies of patients with chronic fatigue syndrome (CFS) from northern Nevada are summarized. Physicians caring for these patients have estimated that greater than 400 patients with CFS from northern Nevada and nearby communities in California were identified

	Reno 89557.			between 1984 and 1988. As a result of these studies, a cluster of clinical and laboratory features associated with the illness in moderately to severely affected patients has been identified: profound fatigue of prolonged duration; cervical lymphadenopathy; recurrent sore throat and/or symptoms of influenza; loss of cognitive function manifested by loss of memory and loss of ability to concentrate; myalgia; impairment of fine motor skills; abnormal findings on magnetic resonance imaging brain scan; depressed level of antibody to Epstein-Barr virus (EBV) nuclear antigen; elevated level of antibody to EBV early antigen restricted component; elevated ratio of CD4 helper to CD8 suppressor cells; and strong evidence of association of this syndrome with infection with human herpesvirus 6. More-serious and longer-lasting neurologic impairments, including seizures, psychosis, and dementia, have also been observed in some of these patients.
David AS, Wessely S, Pelosi AJ.	King's College Hospital, London.	Chronic fatigue syndrome: signs of a new approach.	Br J Hosp Med 1991 Mar;45(3):158-63 comment in: Br J Hosp Med. 1991 Oct;46(4):270	Persistent media highlighting of the plight of patients suffering from severe fatigue of unknown cause (postviral fatigue syndrome or myalgic encephalomyelitis) has at last been matched by professional attention. Recent research has started to clarify the roles of infective, neuromuscular and psychiatric factors in the illness, but pathophysiological mechanisms remain obscure.
Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, Chrousos GP, Gold PW.	Clinical Neuroendocrinology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland.	Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome.	J Clin Endocrinol Metab 1991 Dec;73(6):1224-34	Chronic fatigue syndrome is characterized by persistent or relapsing debilitating fatigue for at least 6 months in the absence of a medical diagnosis that would explain the clinical presentation. Because primary glucocorticoid deficiency states and affective disorders putatively associated with a deficiency of the arousal-producing neuropeptide CRH can be associated with similar symptoms, we report here a study of the functional integrity of the various components of the hypothalamic-pituitary-adrenal axis in patients meeting research case criteria for chronic fatigue syndrome. Thirty patients and 72 normal volunteers were studied. Basal activity of the hypothalamic-pituitary-adrenal axis was estimated by determinations of 24-h urinary free cortisol-excretion, evening basal plasma total and free cortisol concentrations, and the cortisol binding globulin-binding capacity. The adrenal cortex was evaluated indirectly by cortisol responses during ovine CRH (oCRH) stimulation testing and directly by cortisol responses to graded submaximal doses of ACTH. Plasma ACTH and cortisol responses to oCRH were employed as a direct measure of the functional integrity of the pituitary corticotroph cell. Central CRH secretion was assessed by measuring its level in cerebrospinal fluid. Compared to normal subjects, patients demonstrated significantly reduced basal evening glucocorticoid levels (89.0 +/- 8.7 vs. 148.4 +/- 20.3 nmol/L; P less than 0.01) and low 24-h urinary free cortisol excretion (122.7 +/- 8.9 vs. 203.1 +/- 10.7 nmol/24 h; P less than 0.0002), but elevated basal evening ACTH concentrations. There was increased adrenocortical sensitivity to ACTH, but a reduced maximal response [F(3.26, 65.16) = 5.50; P = 0.0015]. Patients showed attenuated net integrated ACTH responses to oCRH (128.0 +/- 26.4 vs. 225.4 +/- 34.5 pmol/L.min, P less than 0.04). Cerebrospinal fluid CRH levels in patients were no different from control values (8.4 +/- 0.6 vs. 7.7 +/- 0.5 pmol/L; P = NS). Although we cannot definitively account for the etiology of the mild glucocorticoid deficiency seen in chronic fatigue syndrome patients, the enhanced adrenocortical sensitivity to exogenous ACTH and blunted ACTH responses to oCRH are incompatible with a primary adrenal insufficiency. A pituitary source is also unlikely, since basal evening plasma ACTH concentrations were elevated. Hence, the data are most compatible with a mild central adrenal insufficiency secondary to either a deficiency of CRH or some other central stimulus to the pituitary-adrenal axis. Whether a mild glucocorticoid deficiency or a putative deficiency of an arousal-producing neuropeptide such as CRH is related to the clinical symptomatology of the chronic fatigue syndrome remains to be determined.
Demitrack MA, Greden JF. Review Review, Tutorial		Chronic fatigue syndrome: the need for an integrative approach.	Biol Psychiatry 1991 Oct 15;30(8):747-52	
Deulofeu R, Gascon J, Gimenez N, Corachan M.		Magnesium and chronic fatigue syndrome.	Lancet 1991 Sep 7;338(8767):641 comment on: Lancet. 1991 Mar 30;337(8744):757-60	
Dille JR.		Chronic fatigue syndrome.	Aviat Space Environ Med 1991 Oct;62(10):1008-9	

Evans AS.	Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510.	Chronic fatigue syndrome: thoughts on pathogenesis.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S56-9	Studies have shown that a proportion of patients with severe chronic infection due to Epstein-Barr virus (EBV) lack antibody to a component of EBV nuclear antigen. However, it is not clear whether this circumstance is one of cause or effect in regard to the pathogenesis of chronic fatigue syndrome (CFS); it is clearly not pathognomonic since it also occurs in persons infected with the human immunodeficiency virus and--rarely--in those with other EBV-related conditions. Stress and depression may be other pathogenetic mechanisms that could reactivate EBV and lead to CFS; examples of this phenomenon are given. The syndrome might also follow certain other viral infections as part of a process that has been called postinfectious neurasthenia. Currently, the cause(s) and cure of CFS, a common and distressing syndrome, are enigmatic and require multidisciplinary study.
Fark AR.	Department of Family Medicine, Burns Clinic Medical Center, Michigan, Royne City, MI 49712.	Infectious mononucleosis, Epstein-Barr virus, and chronic fatigue syndrome: a prospective case series.	J Fam Pract 1991 Feb;32(2):202, 205-6, 209 comment in: J Fam Pract. 1991 May;32(5):456	Epstein-Barr viral infection, specifically infectious mononucleosis, typically has a more protracted course than other acute viral illnesses. Some recent observers have additionally suggested the possibility that Epstein-Barr virus (EBV) is the etiologic infectious agent in chronic fatigue syndrome, based on the finding of higher proportions of elevated antibodies to the EBV early antigen in some patients complaining of chronic fatigue. Straus et al reported on 23 patients with chronic fatigue, 83% of whom exhibited persistently elevated antibodies in modest titer to the early antigen. Ten of these patients had never fully recovered from an episode of acute infectious mononucleosis. Other studies had noted similar associations between persistently elevated antibodies to EBV-specific antigens and chronic symptoms in patients who presented with chronic symptoms after mononucleosis. Three important antigen complexes, demonstrable by immunofluorescence procedures, are expressed in EBV-infected cells. The early antigen is thought to function perhaps in early replication of viral DNA. A late antigenic complex, the viral capsid antigen, may represent, in addition to structural capsid proteins, components of the viral enzymatic machinery for late phases of replication or transformation. The Epstein-Barr nuclear antigen is felt to function in viral transformation of host cells.
Furman JM.	Department of Otolaryngology, University of Pittsburgh, Pennsylvania.	Testing of vestibular function: an adjunct in the assessment of chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S109-11	Patients with chronic fatigue syndrome (CFS) often complain of dysequilibrium that is nonspecific. The basis of this complaint is unknown but may be related to vestibular system abnormalities, in that an association between inner-ear deficits and infectious mononucleosis has been established in the medical literature. An overview of quantitative vestibular function testing is given, including vestibulo-ocular and vestibulospinal tests. The basic principles of caloric and rotational testing are provided, including the interaction between vision and the vestibular system. Moving-platform posturography is described. Preliminary results from quantitative vestibular function testing of a small group of individuals with CFS are provided.
Goldenberg DL.	Newton-Wellesley Hospital, Newton, Massachusetts.	Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome.	Curr Opin Rheumatol 1991 Apr;3(2):247-58	There continues to be an emerging body of literature related to fibromyalgia and the related conditions chronic fatigue syndrome and myofascial pain. During the past year, the most notable contributions included a large multicenter study providing new diagnostic criteria for the classification of fibromyalgia and clinical studies describing the overlap of fibromyalgia, chronic fatigue syndrome, and myofascial pain. Pathophysiologic studies were often preliminary and uncontrolled but the focus of these studies on abnormal nociception, neurohormones, and muscle metabolism provides an exciting hypothesis to unify pain, fatigue, and sleep disturbances, the primary symptoms of fibromyalgia. Unfortunately, new therapeutic trials were neither innovative nor especially encouraging.
Gorenssek MJ.	Department of Infectious Disease, Cleveland Clinic Florida, Ft. Lauderdale, Florida.	Chronic fatigue and depression in the ambulatory patient.	Prim Care 1991 Jun;18(2):397-419	Fatigue, pain, and emotional upset remain the most common problems affecting humanity and for which we still know so very little. Chronic fatigue syndrome is most likely a number of as yet unproven various undifferentiated illnesses that are exceedingly difficult to distinguish from depression. There probably is a subset of patients with CFS who do have true immune dysfunction and persistent viral infection, and this particular group of patients should be further investigated. This group is the minority of patients who present with chronic fatigue. Although chronic fatigue syndrome may be the result of an organic illness in psychologically susceptible individuals, it remains most important to assess underlying psychologic factors that then need to be addressed. These factors may very likely have a profound effect on immune function, but more research is needed in this area. The diagnostic evaluation of patients with chronic fatigue syndrome should initially focus on causes for fatigue other than Epstein-Barr viral infection. Significant underlying medical conditions should be ruled out, and extensive inquiry into symptoms suggestive of depression and anxiety should be aggressively pursued. Treatment should include psychiatric support and counseling, good nutrition,

				adequate rest, and a gradual increase in activity. Anti-inflammatory agents and serotonin-replenishing antidepressants are helpful when muscle pain and tenderness are a major part of the patient's symptoms. Psychoactive drugs are useful when indicated. Low doses of antidepressants such as doxepin (10-25 mg at night) are generally well tolerated and have shown efficacy in numerous patients, although there are no reports of controlled trials.
Goudsmit EM, Macintyre A, Sullivan M.		Chronic fatigue syndrome.	Br J Gen Pract 1991 Nov;41(352):479-80 comment in: Br J Gen Pract. 1992 Jan;42(354):39-40 comment on: Br J Gen Pract. 1991 Aug;41(349):339-42	
Gracious B, Wisner KL.	Department of Psychiatry, University of Pittsburgh School of Medicine, PA 15213.	Nortriptyline in chronic fatigue syndrome: a double blind, placebo-controlled single case study.	Biol Psychiatry 1991 Aug 15;30(4):405-8	
Grafman J, Johnson R Jr, Scheffers M.	Cognitive Neuroscience Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892.	Cognitive and mood-state changes in patients with chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S45-52	In this paper the cognitive and psychiatric impairments associated with chronic fatigue syndrome (CFS) and related disorders are reviewed. It is concluded that while acute mononucleosis and infection with Epstein-Barr virus occasionally result in impaired cognition, such changes have not yet been objectively verified in patients with CFS. However, when patients with CFS are carefully studied, concurrent or premorbid psychiatric disorders are revealed at a greater than chance level. Finally, some suggestions are offered regarding improved neuropsychological assessment of fatigue, concentration, and attention for patients with CFS. The findings to date, while suggesting that psychological predisposition may play a role in the expression of CFS, are still inconclusive regarding the etiology of CFS.
Grufferman S.	Department of Clinical Epidemiology and Preventive Medicine, University of Pittsburgh School of Medicine, Pennsylvania 15261.	Issues and problems in the conduct of epidemiologic research on chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S60-7	The epidemiologic research approach is perhaps most appropriate for initial studies of chronic fatigue syndrome since the syndrome is vaguely defined, scientific knowledge about it is limited, and an infectious etiology is suspected. Several priority needs appropriate for epidemiologic research are identified, including a refinement of diagnostic criteria; a greater understanding of the natural history of the syndrome; basic incidence, prevalence, and mortality statistics; information on whether asymptomatic cases exist; etiologic studies of possible heterogeneity of cases; investigations of clusters of cases; and determinations of whether patients with the syndrome have an increased risk of malignancy. Because of the lack of cogent etiologic hypotheses regarding the syndrome, case-control studies are identified as a high priority for research. The many difficulties encountered in conducting such research are discussed and approaches to dealing with these problems are suggested.
Gupta S, Vayuvegula B.	Division of Basic and Clinical Immunology, University of California, Irvine 92717.	A comprehensive immunological analysis in chronic fatigue syndrome.	Scand J Immunol 1991 Mar;33(3):319-27	A detailed analysis of cell-mediated and antibody-mediated immunity was performed in 20 CDC-defined patients with chronic fatigue syndrome (CFS) and 20 age- and sex-matched healthy controls. CD3+, CD4+, CD8+, and CD20+ lymphocytes were comparable in two groups. Natural killer cells as defined by CD16, CD56 and CD57 antigens were significantly reduced in CFS. A significant increase in the proportions of CD4+ ICAM 1+ T cells was observed in CFS. Monocytes from CFS displayed increased density (as determined by mean fluorescence channel numbers) of intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function associated antigen 1 (LFA-1), but showed decreased enhancing response to recombinant interferon-gamma in vitro. The lymphocyte DNA synthesis in response to phytohaemagglutinin (PHA), Concanavalin A (Con A) and pokeweed mitogen (PWM) was normal but the response to soluble antigens was significantly reduced. Serum IgM, IgG, IgA, and IgG subclasses were normal. In vivo specific antibody response to pneumococcus vaccine was depressed in CFS. Forty percent of patients showed titres of anti-human herpes virus 6 (anti-HHV-6) antibody higher than that in the controls (greater than or equal to 1/80). These data suggest immunological dysfunction in patients with chronic fatigue syndrome. The significance of these observations is discussed.
Hawton KE, Hengeveld MW.	Warneford Hospital, Psychiatrische	[Chronic fatigue syndrome; psychiatric aspects].[article in	Ned Tijdschr Geneesk 1991 Oct 26;135(43):2014-7	

	Universiteitskliniek, Oxford, Engeland.	Dutch]		
Hayden SP.	Department of Internal Medicine, Cleveland Clinic Foundation, Ohio 44195.	A practical approach to chronic fatigue syndrome.	Cleve Clin J Med 1991 Mar-Apr;58(2):116-20	Chronic fatigue may have several physical causes, but a psychiatric condition is often involved. A substantial minority of patients are not diagnosed by conventional tests and do not respond to antidepressant therapy. These patients should be referred for psychiatric opinion or observed for new developments. Extensive virologic testing and unorthodox treatment approaches have no scientific basis at present. Claims of dramatic new diagnostic tests or therapy should be treated with caution because of the long history of unsuccessful attempts to categorize chronic fatigue into one diagnosis and the strong placebo effect shown in controlled trials.
Hick JF.		The etiology of chronic fatigue syndrome.	Minn Med 1991 Sep;74(9):7-8 comment on: Minn Med. 1991 May;74(5):21-6	
Hickie I, Lloyd A, Wakefield D.		Chronic fatigue syndrome and depression.	Lancet 1991 Apr 13;337(8746):922-3 comment on: Lancet. 1991 Jan 19;337(8734):160-2	
Hilgers A, Krueger GR, Lembke U, Ramon A.	International Institute of Immunopathology, Inc. Cologne, Washington, DC.	Postinfectious chronic fatigue syndrome: case history of thirty-five patients in Germany.	In Vivo 1991 May-Jun;5(3):201-5	Thirty-five patients with chronic fatigue syndrome according to the criteria of Holmes were followed for periods of up to eight years. The most frequent symptoms were severe fatigue, arthralgias and myalgias, recurrent oropharyngitis and various psychiatric disorders. More than half of the patients suffered from neuropathy, lymphadenopathy, gastrointestinal complaints and recurrent low-grade fever. Recurrent or persistent activity of human herpesvirus -6 infection was seen in 73% of the patients and of Epstein-Barr virus in 34.4%. In addition, various other infections were diagnosed at lower frequency. Initial routine immunologic screening revealed various types of deficiencies, these were yet inconsistent and variable when different patients were compared with each other. Tentative treatments included in immunoglobulins, nonspecific immunostimulation and virostatic drugs. No consistently positive results were obtained with any treatment schedule although immunoglobulins appeared the most efficient measure. In addition, psychologic care of the patients is indicated, since disturbances in the psycho-neuroimmunologic regulation may play a significant role in the pathogenesis of the disease.
Holmes GP.	Epidemiology Office, Centers for Disease Control, Atlanta, Georgia 30333.	Defining the chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S53-5	The recently published working definition of the chronic fatigue syndrome (CFS) is a necessary first step toward a consistent effort to research this controversial illness. Before this definition was developed, cases often were defined vaguely, according to the perceptions and biases of the individual researchers, so that the results of some studies were unclear. However, few specific diagnostic parameters for CFS exist, and the new definition may not delineate a single clinicopathologic entity. Future efforts at researching this illness should be aimed at identifying parameters that differentiate CFS from psychiatric conditions such as major depression and from other defined chronic diseases. Because CFS may be the result of multiple disease processes, the separate study of well-defined subgroups of patients with CFS is appropriate. Such subgroups of patients are probably more likely to have common pathogenetic features than are patients with CFS as a whole group.
Ho-Yen DO, McNamara I.	Raigmore Hospital, Inverness.	General practitioners' experience of the chronic fatigue syndrome.	Br J Gen Pract 1991 Aug;41(349):324-6 comment in: Br J Gen Pract. 1991 Nov;41(352):480	In order to examine the prevalence of patients with symptoms fulfilling the criteria for the chronic fatigue syndrome an extensive survey was carried out of general practitioners on 10 local government lists in two health boards (91% response rate). At the same time practitioners' attitudes to the syndrome and their experience in terms of workload and the characteristics of patients affected were documented. The majority of general practitioners (71%) accepted the existence of chronic fatigue syndrome, but 22% were undecided. The doctors reported a prevalence among their patients of 1.3 per 1000 patients (range 0.3-2.7 for the 10 areas) with a peak in the 30-44 years age group. Female patients were more commonly affected than males (sex ratio 1.8:1.0), but the severity of illness and the use of general practitioner's time was the same among male and female patients. Patients in occupations where they were exposed to infection were affected (teachers and students, 22% of sample; hospital workers, 7%), but many patients were unskilled (8%) and skilled workers (9%). Patients suffering from the chronic fatigue syndrome appear to be a real and distinct group for general practitioners and may represent a

				substantial part of the workload of doctors in particular areas.
Hyde BM.		Myalgic encephalomyelitis (chronic fatigue syndrome): an historic perspective.	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:5-8	
Joncas JH.		Search for an association between Epstein-Barr virus infection and the chronic fatigue syndrome.	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:43-7	
Jones JF, Streib J, Baker S, Herberger M.	Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206.	Chronic fatigue syndrome: I. Epstein-Barr virus immune response and molecular epidemiology.	J Med Virol 1991 Mar;33(3):151-8	Patients with chronic fatigue syndrome were compared to healthy seropositive control subjects in an open study and a case-control study analyzing spontaneous transformation rates of peripheral blood lymphocytes, EBV viral genome characteristics as determined by DNA restriction fragment polymorphisms, and antibody production by Western blot analysis. Thirty percent of patients versus 8% of control subjects underwent spontaneous transformation in the two studies. Viral genome patterns were overall similar to one another, with polymorphisms frequently present in BamHI B', K, H, and Y fragments. Only one line was found with the EBNA-2B genotype. Nineteen lines were found to contain viral DNA in the linear form suggesting active lytic replication. Western blot studies suggested that ill subjects made antibodies to lytic proteins more frequently than did healthy control subjects. Lack of control of EBV outgrowth in vitro is correlated with antibody evidence of active infection in vivo in some patients with chronic fatigue syndrome.
Jones JF.	Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206.	Serologic and immunologic responses in chronic fatigue syndrome with emphasis on the Epstein-Barr virus.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S26-31	Although patients with chronic fatigue syndrome (CFS) can be diagnosed by clinical criteria, the lack of specific laboratory criteria delays or prevents the diagnosis and contributes to the quasi-disease status of the syndrome. A resurgence of interest in the syndrome has followed reports suggesting that CFS may be associated with chronic active infection due to the Epstein-Barr virus. Analysis of reports to date shows that the mean titers of antibodies to viral capsid antigen and to early antigen are greater for patients with CFS than for healthy individuals; this is particularly evident in cases for which serial samples were tested. However, these differences do not prove the cause of CFS. Cell-mediated immune responses in patients with CFS vary from study to study, and the number and function of natural killer cells in those patients are the most variable factors. Rates of isolation of virus from saliva do not differ, but in one comparison study with a large number of subjects, more lymphocytes that contained virus were isolated from patients than from controls. Other viruses, such as the Coxsackie B virus, have been implicated as causes of CFS in studies from Great Britain. The use of a working definition of CFS and standardized tests to address abnormalities revealed by laboratory tests among homogeneous populations should allow determination of useful tests for the diagnosis of CFS and studies of its mechanisms.
Josephs SF, Henry B, Balachandran N, Strayer D, Peterson D, Komaroff AL, Ablashi DV.		HHV-6 reactivation in chronic fatigue syndrome.	Lancet 1991 Jun 1;337(8753):1346-7	
Katon WJ, Buchwald DS, Simon GE, Russo JE, Mease PJ.	Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle 98195.	Psychiatric illness in patients with chronic fatigue and those with rheumatoid arthritis.	J Gen Intern Med 1991 Jul-Aug;6(4):277-85 comment in: J Gen Intern Med. 1991 Jul-Aug;6(4):378-9	OBJECTIVES: To identify psychiatric differences between patients with chronic fatigue and those with rheumatoid arthritis and to investigate whether patients meeting Centers for Disease Control (CDC) criteria for chronic fatigue syndrome (CFS) can be differentiated from patients with chronic fatigue on measures of disability and psychosocial distress. DESIGN: Cross-sectional study comparing 98 patients with chronic fatigue with 31 patients with rheumatoid arthritis on structured psychiatric interviews and patient questionnaires. Nineteen patients meeting CDC criteria for CFS were compared with 79 patients with chronic fatigue not meeting CDC criteria on questionnaires measuring disability and psychosocial distress. SETTING: Consecutive patients with chronic fatigue were selected from a chronic fatigue clinic at the University of Washington, and 31 consecutive patients with rheumatoid arthritis were sampled from a private rheumatology practice. MAIN RESULTS: Patients with chronic fatigue had a significantly higher prevalence of lifetime major depression and somatization disorder than did patients with rheumatoid arthritis. Patients with chronic fatigue also had a significantly higher prevalence of current and lifetime psychiatric diagnoses. Only 19 of 98 patients with chronic fatigue

				met CDC criteria for CFS. Patients meeting CDC criteria for CFS could not be differentiated from the larger group of patients with chronic fatigue on any study variable. CONCLUSIONS: Patients with chronic fatigue have a significantly higher burden of psychiatric illness than do patients with rheumatoid arthritis. The psychiatric illness preceded the development of chronic fatigue in over half the patients. Centers for Disease Control criteria for CFS did not select a subset of chronic fatigue patients who could be differentiated on disability or psychosocial parameters from patients with chronic fatigue who did not meet CDC criteria.
Komaroff AL, Buchwald D.	Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115.	Symptoms and signs of chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S8-11	This review summarizes the symptoms and signs seen in patients with chronic fatigue syndrome (CFS). It is based on the authors' experience with two cohorts of approximately 510 patients with chronic debilitating fatigue and on the reported experience of other investigators with similar patients. The most characteristic symptoms of CFS are the sudden onset of an infectious-type illness, the subsequent chronic and debilitating fatigue, and postexertional malaise; many patients also have recurrent fevers, pharyngitis, adenopathy, myalgias, sleep disorders, and cognitive impairment.
Kroenke K.	Department of Medicine, Uniformed Services University of Health Sciences, Bethesda, MD 20814.	Chronic fatigue syndrome: is it real?	Postgrad Med 1991 Feb 1;89(2):44-6, 49-50, 53-5 comment in: Postgrad Med. 1991 Nov 15;90(7):23-4	Epstein-Barr virus is no longer considered an important cause of chronic fatigue syndrome. Instead, the disease is probably related to an underlying psychiatric disorder, subtle immunologic dysfunction, or an interaction between these two factors. A carefully taken history, physical examination, and simple laboratory testing are usually sufficient to establish the diagnosis. Therapy with antidepressants or nonsteroidal anti-inflammatory drugs may be effective in selected patients. Thorough follow-up conducted with empathy and optimism is important in all cases.
Krueger GR, Ablashi DV, Josephs SF, Salahuddin SZ, Lembke U, Ramon A, Bertram G.	Immunopathology Laboratory, University of Cologne, F.R.G.	Clinical indications and diagnostic techniques of human herpesvirus-6 (HHV-6) infection.	In Vivo 1991 May-Jun;5(3):287-95	The sixth member of the human herpesvirus family, HHV-6, causes early childhood infection with subsequent latency and antibody prevalence of about 60-80%. Active infection is related to a number of acute and chronic diseases such as exanthem subitum, certain cases of infectious mononucleosis and other immunoproliferative syndromes, autoimmune disorders and so-called postinfectious chronic fatigue syndrome. The clinical diagnosis of HHV-6 associated diseases requires detailed clinical differential diagnostic procedures and meticulous serological testing with exclusion of other herpesvirus infections or cross-reactivity between such infections. Diagnostic efforts, however, are warranted by certain indications for therapeutic intervention. The current review summarizes indications, techniques and limitations for the serological diagnosis of HHV-6 infection.
Krupp LB, Mendelson WB, Friedman R.	Department of Neurology, State University of New York, Stony Brook 11794.	An overview of chronic fatigue syndrome.	J Clin Psychiatry 1991 Oct;52(10):403-10 comment in: J Clin Psychiatry. 1992 Aug;53(8):296	BACKGROUND: Psychological and immunologic factors both appear to contribute to chronic fatigue syndrome (CFS). By comparing CFS with other disorders in which fatigue is a prominent symptom, the association between fatigue, psychological vulnerability, depression, and immune function may be further defined. Recent data from psychological, neurologic, and immunologic studies that address these issues are reviewed. METHOD: Articles and abstracts covering CFS and related topics of fatigue, depression, and postinfectious syndromes were identified through MEDLINE and Index Medicus (1980-1990) and by bibliographic review of pertinent review articles. RESULTS: The 1988 definition of CFS by the Centers for Disease Control encompasses several conditions in which the major characteristic is severe fatigue associated with constitutional symptoms. Several studies have identified immune dysfunction in CFS patients, but the specificity of these findings remains unclear. Most studies have shown that CFS patients, compared with other patients with chronic medical illness, experience more disabling fatigue. Some investigators have found a higher incidence of concurrent and past psychiatric illness in CFS patients compared with other medical patients, thereby suggesting an underlying psychopathology in CFS. However, other studies have not found a higher than expected incidence of past depression in CFS patients and have further shown that many CFS patients have no identifiable psychopathology. CONCLUSION: CFS appears to be a heterogeneous entity. Although there may be a high coincidence of major depression in CFS, a substantial proportion of patients lack any identifiable DSM-III-R psychiatric disorder yet still manifest the syndrome, thereby suggesting it has an autonomous entity. Despite the evolving nature of our current understanding of CFS, a rational diagnostic and therapeutic approach to CFS is possible.
Kulig JW.		Chronic Fatigue Syndrome and Fibromyalgia in Adolescence.	Adolesc Med 1991 Oct;2(3):473-484	A complaint of persistent, debilitating fatigue in an adolescent, accompanied by symptoms that meet the recently adopted criteria for chronic fatigue syndrome (CFS), presents a difficult challenge for the clinician. This article describes the diagnostic criteria for CFS and fibromyalgia, and discusses the epidemiology, etiology, and management of these conditions.

Kundu SK, Ahronheim GA, Menezes J.		Immunodysregulation and chronic fatigue syndrome.	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:49-50	
Kutemeyer M.		[Comments on the review by Wilfrid A. Nix. Chronic fatigue syndrome--a new disease picture]?[article in German]	Nervenarzt 1991 Jan;62(1):64-6	
Lam RW.	Department of Psychiatry, University of British Columbia, Vancouver.	Seasonal affective disorder presenting as chronic fatigue syndrome.	Can J Psychiatry 1991 Nov;36(9):680-2	Although operational criteria have been recently proposed to better define chronic fatigue syndrome (CFS), it remains a controversial diagnosis. There are many overlapping symptoms between CFS and major depression. The author presents two patients with seasonal affective disorder, who responded to phototherapy and had previously been diagnosed as CFS. Because of the consequences of treatment, seasonal and non seasonal depression need to be ruled out in patients with chronic fatigue symptoms.
Landay AL, Jessop C, Lennette ET, Levy JA.	Department of Immunology/Microbiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.	Chronic fatigue syndrome: clinical condition associated with immune activation.	Lancet 1991 Sep 21;338(8769):707-12	There is much conflicting immunological and viral data about the causes of chronic fatigue syndrome (CFS); some findings support the notion that CFS may be due to one or more immune disorders that have resulted from exposure to an infectious agent. In the present study, flow cytometry and several different monoclonal antibodies recognising T, B, and natural killer (NK) cell populations as well as activation and cell adhesion antigens were used to study 147 individuals with CFS. Compared with healthy controls, a reduced CD8 suppressor cell population and increased activation markers (CD38, HLA-DR) on CD8 cells were found. The differences were significant ($p = 0.01$) in patient with major symptoms of the disease. These immunological indices were not observed in 80 healthy individuals, in 22 contacts of CFS patients, or in 43 patients with other diseases. No correlation of these findings in CFS patients with any known human viruses could be detected by serology. The findings suggest that immune activation is associated with many cases of CFS.
Lane TJ, Manu P, Matthews DA.	Department of Medicine, University of Connecticut School of Medicine, Farmington 06032.	Depression and somatization in the chronic fatigue syndrome.	Am J Med 1991 Oct;91(4):335-44 comment in: Am J Med. 1992 Jun;92(6):710 Am J Med. 1994 May;96(5):485-6	PURPOSE: To report the prevalence, clinical features, and diagnostic associations of the proposed chronic fatigue syndrome (CFS) in a cohort of patients with chronic fatigue and to assess the usefulness of a structured psychiatric interview for detecting previously unrecognized psychiatric morbidity in patients with CFS. PATIENTS AND METHODS: A consecutive sample of 200 adult patients with a chief complaint of chronic fatigue was prospectively evaluated in a referral-based clinic within a university general medicine practice. All patients received a thorough medical history, physical examination, diagnostic laboratory testing, and portions of the Diagnostic Interview Schedule, version III-A. The criteria for CFS were applied, and patients with CFS were compared with matched control subjects from the inception cohort. RESULTS: The 60 patients with CFS had similar likelihoods of current psychiatric disorders (78% versus 82%), active mood disorders (73% versus 77%), and preexisting psychiatric disorders (42% versus 43%) when compared with fatigued control subjects. Patients with CFS were more likely to have somatization disorder (p less than 0.001) and to attribute their illness to a physical cause (p less than 0.005) than fatigued controls. Patients with CFS also displayed functional symptoms, often lifelong, which are not part of the case definition of CFS. Depressive features in patients with CFS were similar to those of control subjects, but a trend toward suicidal behavior was noted. CONCLUSIONS: Patients with CFS have a high prevalence of unrecognized, current psychiatric disorders, which often predate their fatigue syndrome. Assessment of patients with CFS should include a structured psychiatric evaluation.
Leventhal LJ, Naides SJ, Freundlich B.	Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia.	Fibromyalgia and parvovirus infection.	Arthritis Rheum 1991 Oct;34(10):1319-24	An infectious cause of fibromyalgia (FM) has been hypothesized based upon the observed similarity of this entity and chronic fatigue syndrome. Three patients developed symptoms of FM after documented episodes of acute parvovirus B19 infections. B19 antibody determinations were obtained approximately 1 month after the symptoms began; both IgM and IgG titers were positive at that time. All 3 patients met criteria for FM. Polysomnography performed on 2 of the patients revealed profound alpha-wave intrusion throughout nonrapid eye movement sleep. A more careful search for viral infections in FM patients whose symptoms appear following a "flu-like" illness appears warranted.
Lewis SF, Haller RG.	Department of Physiology, University of Texas Southwestern Medical Center,	Physiologic measurement of exercise and fatigue with special reference to chronic	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S98-108	Oxidative metabolism is the major source of energy for muscle activity, and maximal oxygen uptake (VO_{2max}), the product of maximal cardiac output and maximal arteriovenous oxygen difference, indicates individual capacity for oxidative metabolism and performance of exercise by the large

	Dallas.	fatigue syndrome.		muscles. Strength, a function of muscle cross-sectional area, motor-unit recruitment, and neuromuscular coordination, is the ability to develop force in a single, brief, maximal-effort voluntary contraction of rested muscle. Weakness is a diminished ability of rested muscle to exert maximal force. Fatigue is a loss of maximal force-generating capacity that develops during muscular activity, likely originates within muscle itself, and persists until muscle is fully recovered. Individual perception of motor effort can be determined with standardized rating scales. These concepts are discussed in detail, their relevance to the pathophysiology of exercise in chronic fatigue syndrome is analyzed, and a general strategy of exercise evaluation pertinent to chronic fatigue syndrome is presented.
Lloyd A, Hickie I, Brockman A, Dwyer J, Wakefield D.		Cytokine levels in serum and cerebrospinal fluid in patients with chronic fatigue syndrome and control subjects.	J Infect Dis 1991 Nov;164(5):1023-4	
Lloyd AR, Gandevia SC, Hales JP.	Department of Clinical Neurophysiology, Prince Henry Hospital, Sydney, Australia.	Muscle performance, voluntary activation, twitch properties and perceived effort in normal subjects and patients with the chronic fatigue syndrome.	Brain 1991 Feb;114 (Pt 1A):85-98	The decrease in maximal force-generating capacity, the degree of central activation of the muscle, and the subjective perception of effort were measured during prolonged submaximal isometric exercise in 12 male patients suffering from the 'chronic fatigue syndrome' and 13 naive, healthy male subjects. Maximal voluntary isometric torque generated by the elbow flexors was measured before, and at 5 min intervals during an endurance sequence of 45 min of repetitive isometric contractions (6 s duration, 4 s rest interval) producing 30% of the initial maximal voluntary torque. Electrical stimuli were also delivered to the elbow flexors to measure the contractile force in the intervals between voluntary contractions. The degree of central motor activation during maximal voluntary contractions was assessed using a sensitive method of twitch interpolation. In addition, the perceived effort required to achieve the target submaximal contractions was recorded using a standardized self-report scale. A high degree of central activation was achieved in maximal contractions during the endurance sequence both in the patients (mean of maximal force 93.6%; SD 7.8%), and in the control subjects (mean 90.9%; SD 9.5%). The relative torque produced by either voluntary or electrically stimulated contractions was not significantly different between patients and control subjects throughout the test. There was no significant difference in the perceived exertion between the patients and control subjects. These findings support the concept that neither poor motivation, nor muscle contractile failure is important in the pathogenesis of 'fatigue' in patients with the chronic fatigue syndrome.
Lopis R.		A personal encounter with a mystery illness.	Aust Fam Physician 1991 Mar;20(3):316-7	I urge all practitioners to accept that 'chronic fatigue' patients have genuine symptoms. This disease can cause depression, but for most patients it is not caused by depression. I acknowledge that a depressed patient can develop the chronic fatigue syndrome in the same way that they can contract any other disease. If you are unable to diagnose a patient with these symptoms please refer them to a centre specialising in this devastating and poorly understood disease.
Lynch S, Main J, Seth R.		Definition of chronic fatigue syndrome (CFS)	Br J Psychiatry 1991 Sep;159:439-40 comment in: Br J Psychiatry. 1992 Jan;160:127-8 comment on: Br J Psychiatry. 1991 May;158:717	
Lynch S, Seth R, Montgomery S.	St Mary's Hospital Medical School, London.	Antidepressant therapy in the chronic fatigue syndrome.	Br J Gen Pract 1991 Aug;41(349):339-42 comment in: Br J Gen Pract. 1991 Nov;41(352):479-80 Br J Gen Pract. 1991 Nov;41(352):480	The chronic fatigue syndrome is a condition receiving increasing recognition. Symptoms of depression are not infrequent and may be persistent and severe enough to warrant treatment. The controversy over the use of antidepressant therapy in this condition may present a dilemma for the general practitioner considering possible treatments. This paper draws on the literature and on the authors' own observations of patients with the chronic fatigue syndrome to suggest guidelines for the use of antidepressant therapy.
Malleson PN.	Research Centre, University of British Columbia, Vancouver, Canada.	Pain syndromes, disability, and chronic disease in childhood.	Curr Opin Rheumatol 1991 Oct;3(5):860-6	Childhood disability and chronic disease are common, and their prevalence is increasing as children survive with conditions that were previously fatal. It is important that physicians in training learn about disability and handicap, and the functioning of multidisciplinary teams to manage these problems. Chronic ill-health is often very expensive to manage, and some serious and creative thinking about the best way to fund such health care is urgently needed. Pediatric rheumatologists are involved with the

				care of many children with chronic and recurrent musculoskeletal pain; however, they have not perhaps focused enough research effort on the investigation of pain and its management. Whether reflex neurovascular dystrophy, fibromyalgia, and chronic fatigue syndrome are part of a disease continuum is unclear, but it seems probable that psychosocial problems are often important contributing factors in all three conditions. Immunoglobulin subclass deficiencies are being increasingly delineated, occurring in chronic fatigue syndrome as well as many other disease states. Their clinical relevance still remains, for the most part, uncertain. Short stature occurs in many chronic illnesses, and the role of growth hormone treatment in these conditions is beginning to be investigated.
Mantysaari M.		Aerobic work capacity in chronic fatigue syndrome.	BMJ 1991 Jan 5;302(6767):50 comment on: BMJ. 1990 Oct 27;301(6758):953-6	
Matthews DA, Lane TJ, Manu P.	Division of General Medicine, University of Connecticut School of Medicine, Farmington.	Antibodies to Epstein-Barr virus in patients with chronic fatigue.	South Med J 1991 Jul;84(7):832-40	To clarify the role of Epstein-Barr virus (EBV) infection and the value of EBV antibody testing in evaluating patients with chronic fatigue, we studied 200 consecutive patients with chronic fatigue (mean duration, 9 years). Complete EBV serologic panels were obtained for 154 patients, 35 (23%) of whom met serologic or clinical criteria for chronic or reactivated EBV infection. We compared these patients with chronic EBV infection (CEBV cases) to 35 age- and sex-matched patients who were selected from the same cohort of fatigued patients but who did not meet the criteria (CEBV control subjects). We found few differences between groups in demographic characteristics, clinical features, and symptoms; CEBV cases were more likely to meet criteria for the proposed chronic fatigue syndrome (14% vs 0%), and to report that they suffered from an influenza-like illness at the onset of their fatigue syndrome (34% vs 12%), that they lost their job because of their fatigue (37% vs 11%), and that their fatigue was improved by recreational activity (26% vs 3%). Physical examination and laboratory testing showed few abnormalities in either group. Psychiatric morbidity was common in both groups, including mood disorders (63% of CEBV cases vs 54% of CEBV controls), anxiety (11% vs 9%) and somatization disorder (9% in each group). We conclude that EBV serologic patterns have little clinical usefulness in evaluating patients with chronic fatigue.
Matthews DA, Manu P, Lane TJ.	Division of General Medicine, University of Connecticut Health Center, Farmington 06030.	Evaluation and management of patients with chronic fatigue.	Am J Med Sci 1991 Nov;302(5):269-77	Chronic fatigue is a common and disabling problem in primary care practice. The differential diagnosis of chronic fatigue is extensive and includes medical disorders, altered physiologic states (eg, pregnancy, exertion), psychiatric disorders, lifestyle derangements, drugs, and controversial entities (eg, chronic candidiasis, food allergies, environmental illness, and chronic fatigue syndrome). The most common diagnoses are psychiatric disorders, including mood, anxiety, and somatoform disorders. A comprehensive approach to diagnosis and management is necessary, including structured psychiatric interviewing, functional assessment, and elicitation of the patient's diagnostic beliefs. Patients often believe they are suffering from an organic medical disorder (eg, viral or immunologic) and resist psychiatric labelling of their symptoms and referral to mental health practitioners. Establishing and maintaining rapport, having a flexible approach, and demonstrating a personal concern for the patient is essential. Drug therapy for specific psychiatric and medical illnesses and cognitive-behavioral approaches for enhancing coping mechanisms are effective.
McBride SJ, McCluskey DR.	Department of Immunology, Queen's University & Royal Victoria Hospital, Belfast, UK.	Treatment of chronic fatigue syndrome.	Br Med Bull 1991 Oct;47(4):895-907	Chronic Fatigue Syndrome is a disorder which is characterised by profound fatigue together with a variety of other subjective clinical features which persist over a prolonged period of time. The aetiology remains at present uncertain and therefore rational therapeutic strategies are difficult to plan. This paper reviews currently used forms of treatment aimed at correcting the possible pathophysiological mechanisms and discusses the problems associated with the management of this condition.
McLaughlin B.		Virology laboratory diagnosis of chronic fatigue syndrome.	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:51-5	
Meadows LM, Walther P, Ozer H.	Division of Medical Oncology, School of Medicine, University of North Carolina, Chapel Hill.	alpha-Interferon and 5-fluorouracil: possible mechanisms of antitumor action.	Semin Oncol 1991 Oct;18(5 Suppl 7):71-6	We have treated 17 patients with 5-fluorouracil (5-FU, 300 mg/m ² /d by continuous ambulatory infusion for 8 weeks) and interferon alfa-2b (escalating doses to cohorts of three to five patients, given subcutaneously on a daily schedule at 2.0, 3.5, 5.0, and 10.0 x 10 ⁶ IU/m ²). The two major toxicities observed were mucositis, which occurred in 10 patients at 2 weeks and required interruption of therapy and 5-FU dose reduction, and chronic fatigue syndrome, which required reduction of the dose of

				interferon alfa-2b. Other toxicities seen included elevation in BUN/creatinine, elevation in liver function tests, alopecia, diarrhea, confusion, and myelosuppression. No toxic deaths occurred. Five responses were observed: two complete responses, two partial responses, and one minor response, all in patients with gastrointestinal malignancy; three of the responding patients had previously failed 5-FU-containing regimens. When we measured 5-FU plasma levels in nine of our patients, they were at or below 1 ng/mL in most patients; however, within 1 hour of administration of interferon alfa-2b, plasma levels rose 16-fold. This elevation of 5-FU levels persisted for at least 24 hours, and could not be accounted for on the basis of altered interleukin-6 levels. When the regimen was tested in eight patients with metastatic renal cell carcinoma as part of a pilot study, three partial responses were observed, and no patient developed disease progression while on treatment. The combination of 5-FU, given by continuous infusion, and interferon alfa-2b, given daily, appears worthy of advancement to phase II trials.
Menezes J, Ablashi DV.		Avenues for research in chronic fatigue syndrome etiology.	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:65-6	
Middleton D, Savage DA, Smith DG.	Northern Ireland Tissue Typing Service, City Hospital, Belfast.	No association of HLA class II antigens in chronic fatigue syndrome.	Dis Markers 1991 Jan-Feb;9(1):47-9	
Mildon CA.		Clinical observations of chronic fatigue syndrome.	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:17-9	
Miller G.	Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut 06510.	Molecular approaches to epidemiologic evaluation of viruses as risk factors for patients who have chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S119-22	One approach to understanding the chronic fatigue syndrome might be to carry out prospective studies of fatigue that occurs following infection with viral diseases of known etiology, such as influenza, hepatitis, and infectious mononucleosis. Among the viral parameters that should be evaluated are virus burden, variation of virus strain, sites of viral replication, and the state of the viral life cycle (e.g., latent or replicative). Immunologic studies should focus on the humoral and cellular responses to defined viral gene products to identify subtle, individual variations in immune recognition of specific viral subcomponents.
Miller JH.		Chronic fatigue syndrome and invalid pensions.	Med J Aust 1991 Feb 18;154(4):293	
Milton JD, Clements GB, Edwards RH.	Department of Medicine, University of Liverpool, UK.	Immune responsiveness in chronic fatigue syndrome.	Postgrad Med J 1991 Jun;67(788):532-7 comment in: Postgrad Med J. 1992 Jan;68(795):66-7	We have endeavoured to find immunological indications of chronic virus infection in patients with chronic fatigue syndrome (myalgic encephalomyelitis) and to investigate immune responsiveness to viruses in such patients in comparison with normal subjects and patients with muscular dystrophy. Levels of circulating IgM immune complexes were elevated (above the 95% normal control range) in 10 (17%) of 58 patients with chronic fatigue syndrome, which was not significantly different from the normal controls or from dystrophy controls (by Mann Whitney U test). Levels of IgG complexes were only increased in 10% of patients. Lymphocyte proliferation in response to concanavalin A (Con A), assessed by increase in 3H-thymidine incorporation, did not differ between 14 patients and 18 normal subjects. The proliferative response to Coxsackie B virus antigen did not differ between chronic fatigue patients and normal subjects when expressed either as an increase in counts or as a stimulation index. Adjustment of the counts in relation to the proliferation response to Con A, as an indication of the overall proliferative response of the cell preparation, did not reveal any hidden difference. IgM antibodies to Coxsackie B viruses were not found in any of 20 patients and in 1 of 20 dystrophy controls. Significant levels of neutralizing antibodies to Coxsackie B viruses 1-5 were found in 6 out of 19 (32%) patients compared with 4 out of 17 (24%) dystrophy controls, which does not differ from currently expected normal incidence. Antibody titres to other respiratory viruses were also not notably different between the patient and control groups.(ABSTRACT TRUNCATED AT 250 WORDS)
Munitz H, Hermesh H.		[Chronic fatigue syndrome, clinical significance].[article in Hebrew]	Harefuah 1991 Feb 1;120(3):164-5	
Murray RS.		Myth of the chronic fatigue syndrome.	West J Med 1991 Jul;155(1):68	

Pagano JS.	Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill 27599-2975.	Detection of Epstein-Barr virus with molecular hybridization techniques.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S123-8	The cord-blood transformation assay remains the standard method for detecting Epstein-Barr virus (EBV) in secretions. However, newer methods are much faster and more sensitive, although most are still regarded as research procedures. The most useful of these are Southern blot hybridization, particularly the variation that employs terminal genomic probe analysis; in situ cytohybridization; and polymerase chain reaction analyses. Use of these methods alone or in combination should disclose the infected cell type, whether the infection is productive or latent, and the presence of multiple strains of EBV. Such information may help establish whether EBV is a causal agent in chronic fatigue syndrome.
Peterson PK, Schenck CH, Sherman R.	Department of Medicine, Hennepin County Medical Center, Minneapolis.	Chronic fatigue syndrome in Minnesota.	Minn Med 1991 May;74(5):21-6 comment in: Minn Med. 1991 Sep;74(9):7-8	Chronic fatigue syndrome (CFS), an illness characterized by debilitating fatigue and a number of associated symptoms, was identified in 135 patients using the case definition provided in 1988. The demographic features of these patients, 97% of whom resided in Minnesota, were similar to those reported elsewhere. About three-fourths of the cases occurred between 1984 and 1989, and in 123 (91.1%), the illness began with what appeared to be an acute infection. Patients had been ill for an average of 4.3 years before enrollment in the study. Fatigue was their most troublesome symptom, although a majority of the patients rated most of the general symptoms and neuropsychological complaints associated with CFS as moderate or severe. Follow-up data obtained on 62 patients one year after initial evaluation revealed that none had completely recovered. However, about 40% reported some improvement in each of the CFS symptoms.
Plummer WP.		Chronic fatigue syndrome.	Br J Gen Pract 1991 Nov;41(352):480 comment on: Br J Gen Pract. 1991 Aug;41(349):324-6	
Pope HG Jr, Hudson JI.	McLean Hospital, Belmont, Massachusetts.	A supplemental interview for forms of "affective spectrum disorder".	Int J Psychiatry Med 1991;21(3):205-32	OBJECTIVE: Recent evidence suggests that a number of psychiatric and medical conditions may be members or candidate members of a larger family of conditions, which we have termed "affective spectrum disorder (ASD)." In order to facilitate further research into this concept, we drafted seven interview modules, using the format of the Structured Clinical Interview for DSM-III-R (SCID), designed to diagnose the following psychiatric and medical disorders: irritable bowel syndrome, narcolepsy, Tourette's disorder, migraine, fibromyalgia, chronic fatigue syndrome, and kleptomania. METHOD: Published operational diagnostic criteria for these seven disorders were sought in the literature. Questions in SCID format were then drafted in accordance with these operational criteria. Draft modules were then sent to experts familiar with each of the disorders and suggestions and revisions from these experts incorporated into the final modules. RESULTS: The complete supplemental interview is presented with this report. Preliminary experience with this interview in more than 100 patients tentatively suggests that it is reliable for diagnosing the disorders in question; however, a formal test-retest reliability assessment is still required. CONCLUSIONS: It is hoped that this supplemental interview, used in conjunction with the SCID, will be helpful in further studies of the epidemiology, pathogenesis, and treatment of these possible forms of affective spectrum disorder.
Purtilo DT.		Dual infections of the immune system in patients with chronic active Epstein-Barr virus infection mimicking chronic fatigue syndrome.	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:29-32	The etiologic bases of CFS are undetermined at the present time. It is very important to distinguish the patients with CFS as defined by the Centers for Disease Control (CDC) case definition of Holmes et al. from patients with physical and laboratory findings suggesting dual infections and/or underlying immunodeficiency. Particularly fruitful might be a longitudinal immunovirologic study of patients who exhibit CFS following a well-documented viral infection.
Radvila A.	Medizinische Universitätsklinik, Inselspital, Bern.	[Intense fatigue in humans. Psychosocial and cultural aspects].[article in German]	Ther Umsch 1991 Nov;48(11):756-61	A differentiation between the normal sensation of tiredness and the symptom "fatigue" is often difficult. Both are influenced by cultural, social, psychological and biological factors, which can lead--interactively--to symptom formation. Psychiatric disorders frequently associated with fatigue are all forms of depression, somatization and anxiety disorders, chronic pain states and drug abuse among many others. In at least 2/3 of patients with the fashionable chronic fatigue syndrome--formerly called neurasthenia--a psychiatric diagnosis can be made, most of them also suffer from many symptoms attributes to the autonomous nervous system. The clinical approach should be cautious avoiding diagnostic and therapeutic overaction and therapy should emerge from a diagnosis properly assessed.
Rand KH.	University of Florida College of Medicine.	Chronic fatigue syndrome: fact or fiction.	Med Sect Proc 1991;:135-44	

Ray C. Review Review, Tutorial		Chronic fatigue syndrome and depression: conceptual and methodological ambiguities.	Psychol Med 1991 Feb;21(1):1-9	
Redmond CK.	Department of Biostatistics, University of Pittsburgh, Pennsylvania 15261.	Analysis of clinical, epidemiologic, and laboratory data on chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S90-3	Much of the research conducted on chronic fatigue syndrome (CFS) is exploratory. The researchers' overall goal is to use clinical, epidemiologic, and laboratory data to provide clues about the etiology of this syndrome. In preparation for this symposium, a review of numerous publications on CFS has indicated that the literature generally does not reflect the application of optimal statistical methods for exploration of data. Whenever the researchers' aim is to generate hypotheses, modern methods designed specifically for exploratory data analysis are likely to provide greater insights into any patterns of data than are the traditional approaches to hypothesis testing. In addition, the use of formal methods of data synthesis for ongoing and future research on CFS is a means of strengthening collaborative efforts and of improving the ability of researchers to interpret the evidence available that relates to specific etiologic factors. The inclusion on the research team of experienced biostatisticians, who would oversee the statistical methods and the development of innovative analyses, is recommended.
Salit IE, Abbey SE, Moldofsky H, Ichise M, Garfinkel PE.		Post-infectious neuromyasthenia (chronic fatigue syndrome): a summary of ongoing studies.	Can Dis Wkly Rep 1991 Jan;17 Suppl 1E:9-12	
Schiraldi O.		[Comments on the "chronic fatigue syndrome"].[article in Italian]	Recenti Prog Med 1991 May;82(5):305	
Schulte PA.	National Institute for Occupational Safety and Health, Centers for Disease Control, Cincinnati, Ohio 45226.	Validation of biologic markers for use in research on chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S87-9	Unresolved aspects of chronic fatigue syndrome can be addressed by research involving biologic markers. These may be any molecular, biochemical, physiological, or other biologic parameter obtainable from biologic specimens. The use of biologic markers in research requires their validation as dependent or independent variables. Additionally, other characteristics of markers such as reliability of assays, background level, confounding factors, interpretations, and legal and ethical implications should be considered before the use of markers in research. A checklist is provided for evaluating a biologic marker before its inclusion in research.
Serra E.		Chronic fatigue syndrome.	Br J Psychiatry 1991 May;158:717 comment in: Br J Psychiatry. 1991 Sep;159:439-40 comment on: Br J Psychiatry. 1990 Apr;156:534-40	
Shafraan SD.	Division of Infectious Diseases, Walter C. MacKenzie Health Sciences Centre, University of Alberta, Edmonton, Canada.	The chronic fatigue syndrome	Am J Med 1991 Jun;90(6):730-9.	The chronic fatigue syndrome (CFS) was formally defined in 1988 to describe disabling fatigue of at least 6 months' duration of uncertain etiology. Reports of CFS have emerged from the United States, Canada, the United Kingdom, Australia, New Zealand, Israel, Spain, and France. The disease primarily affects individuals between 20 and 50 years of age, and there is a preponderance of females. Although a triggering infectious illness is reported by most patients with CFS, there is no convincing evidence causally linking any currently recognized infectious agent to CFS. Multiple minor immunologic aberrations are frequent but inconsistent and of uncertain significance. There is no consistent evidence for myopathy or physical deconditioning. Depression is found in approximately 50% of CFS patients, with depression preceding the physical symptoms in half of the cases. No therapy has been proved effective in controlled clinical trials with prolonged follow-up, although antidepressants have not been formally evaluated. The long-term prognosis of patients with CFS has not been well studied, but CFS appears to be a disease of prolonged duration with considerable morbidity but no mortality. Further research into the pathogenesis and treatment of CFS is necessary.
Sharpe MC, Johnson BA, McCann J.	Warneford Hospital, Oxford.	Mania and recovery from chronic fatigue syndrome.	J R Soc Med 1991 Jan;84(1):51-2	
Simpson LO.		Red cells in the chronic fatigue	Med J Aust 1991 Jun	

		syndrome.	3;154(11):783	
Smalley RV, Anderson SA, Tuttle RL, Connors J, Thurmond LM, Huang A, Castle K, Magers C, Whisnant JK.	University of Wisconsin, Madison.	A randomized comparison of two doses of human lymphoblastoid interferon-alpha in hairy cell leukemia. Wellcome HCL Study Group.	Blood 1991 Dec 15;78(12):3133-41	One hundred thirty-eight patients with hairy cell leukemia were randomized to receive either a dose of 2.0 megaunits (MU)/m ² or a 10-fold lower dose of 0.2 MU/m ² of a highly purified natural alpha-interferon, administered daily for 28 days followed by a three times a week schedule. Ninety-seven of these patients had previously undergone splenectomy, but otherwise none of the patients had received prior therapy for their leukemia. The two doses were comparable in their effect on improving the neutrophil and platelet count, whereas the higher dose had a greater beneficial effect on the hemoglobin level and a greater antileukemic effect on the marrow. Acute toxicity in the form of a flu-like syndrome, neurologic side effects, neutropenia, and the need for platelet transfusions was observed less frequently in the low-dose group, as was the chronic fatigue syndrome. No neutralizing antibody activity was seen in the sera from 61 patients examined. Because of its beneficial effect on the neutrophil and platelet count and a lower degree of toxicity (ie, a superior therapeutic/toxicity ratio), the low dose is recommended as initial therapy in patients with hairy cell leukemia. This therapy may be followed by dose escalation once clinical improvement is observed. Randomized Controlled Trial
Smith JL.	Bascom Palmer Eye Institute, University of Miami School of Medicine, Florida.	Neuro-ocular Lyme borreliosis.	Neurol Clin 1991 Feb;9(1):35-53	Any patient who has a Bell's palsy (unilateral or bilateral), aseptic meningitis, chronic fatigue syndrome, atypical radiculoneuropathy, presenile dementia, atypical myopathy, or symptoms of atypical rheumatoid arthritis should be asked specifically about the following: visits to highly endemic areas, any known tick bites, any skin lesion suggestive of erythema migrans, any history of palpitations or of prior Bell's palsy, aching in joints (especially the knees), paresthesias, chronic fatigue and depression, forgetfulness, and eye problems. Any patient showing a chronic iritis with posterior synechiae, vitritis in one or both eyes, an atypical pars planitis-like syndrome, big blind spot syndrome, and swollen or hyperemic optic discs should be asked the same questions. The physician should send one red-top tube of blood containing 2 to 3 ml serum to Microbiology Reference Laboratory, 10703 Progress Way, Cypress, CA 90630-4714, requesting a Lyme/treponemal panel. For \$90 the patient will receive an RPR test with titer, serum FTA-ABS test, serum Lyme IFA IgG and IgM, and a serum Lyme ELISA test. If these tests are within normal limits and the physician is still suspicious, a Western blot can be ordered on serum. A green top tube with fresh white blood cells sent out by overnight express on a Monday or Tuesday will produce a Lyme PCR and a lymphocyte stimulation test. Finally, R.K. Porschen, director of MRL Laboratory, will provide information on the urine antigen test on an investigational basis. A careful history with emphasis on the specific questions noted above, a complete neuro-ophthalmological and physical examination ruling out other causative problems, and the laboratory studies here discussed will usually provide sufficient data to choose therapy. Much further active research into Lyme borreliosis is an important priority in medicine.
Stern K.		Chronic fatigue syndrome. New disease on the horizon.	J Dent Hyg 1991 Jan;65(1):39-41	
Straus SE.	Medical Virology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892.	History of chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S2-7	Chronic fatigue syndrome is not a new medical condition. For centuries its confusing array of features has been attributed to numerous environmental, metabolic, infectious, immunologic, and psychiatric disturbances. This is a review and critique of many of these alternative diagnoses, sufficient to provide a historical background for current thinking about the disorder.
Strickland MC.	Department of Psychiatry, Cleveland Clinic Florida, Ft. Lauderdale, Florida.	Depression, chronic fatigue syndrome, and the adolescent.	Prim Care 1991 Jun;18(2):259-70	To summarize, CFS and depression present very real problems for adolescent patients, their families, and their physicians. The wealth of symptoms presented may signal the presence of any number of psychiatric or physiologic disorders. As part of the evaluation to rule out other maladies, the physician must identify the developmental issues and life stress events with which patients or their families are struggling. Helping patients to accept psychiatric referral to address these issues is indicated if it is thought that they may be contributing to the onset or maintenance of the symptoms. Referral is also indicated if a protracted clinical course evolves and the patient's normal course of growth and development appears to be in jeopardy.
Sumaya CV.	Department of Pediatrics, University of Texas Health Science Center, San Antonio.	Serologic and virologic epidemiology of Epstein-Barr virus: relevance to chronic	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S19-25	Patients considered to have chronic fatigue syndrome (CFS) have been reported to exhibit an increased antibody response to Epstein-Barr virus (EBV) early antigen complex and capsid antigen, findings that suggest some relationship between EBV and CFS. However, the serologic findings have not been

		fatigue syndrome.		totally consistent among different study groups, and the antibody patterns in asymptomatic individuals may be similar. Moreover, patients with symptomatology indicative of CFS do not appear to have an abnormal burden of EBV in body fluids and manifest only a variable, mild degree of EBV-specific cell-mediated responses. The evidence is growing that the serologic findings of an enhanced EBV state in individuals with CFS-like manifestations, as well as the subsequent reports of increased antibody titers to other viruses, reflect a generalized underlying immunologic dysfunction in these patients. Future studies with criteria-defined CFS study groups in which determinations are made of antibody responses to newly identified EBV-associated nuclear antigen components and distinct EBV proteins in addition to specific virologic and immunologic analyses of EBV may be worthwhile as a means of clarifying the association between EBV and CFS.
Swanink CM, Galama JM, Vercoulen JH, Bleijenberg G, Fennis JF, van der Meer JW.	Instituut Medische Microbiologie, Academisch Ziekenhuis St Radboud, Nijmegen.	[Chronic fatigue syndrome. I. Somatological hypothesis]. [article in Dutch]	Ned Tijdschr Geneeskd 1991 Oct 26;135(43):2005-9 comment in: Ned Tijdschr Geneeskd. 1991 Dec 7;135(49):2347-9 Ned Tijdschr Geneeskd. 1992 Jan 18;136(3):148	
Tavris DE.	Pennsylvania Department of Health.	Criteria for chronic fatigue syndrome.	Pa Med 1991 Jul;94(7):34	
Thase ME.	Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pennsylvania 15213.	Assessment of depression in patients with chronic fatigue syndrome.	Rev Infect Dis 1991 Jan-Feb;13 Suppl 1:S114-8	Assessment of the relationship of depression to chronic fatigue syndrome (CFS) is a complicated but important topic. This relationship may range from the misdiagnostic (i.e., depression misidentified as CFS) to the etiologic (i.e., CFS causes an organic affective syndrome). Assessment should focus on the symptoms and syndromes of depressive disorder, utilization of a single rating scale to assess presumed depression is discouraged, and alternate approaches to classification that allow for symptomatic overlap of a major depressive disorder and CFS are suggested. Careful attention needs to be given to the use of external validating criteria in empiric studies, such as natural history, clinical course (including treatment response), and family history.
Vercoulen JH, Swanink CM, Galama JM, Fennis JF, van der Meer JW, Bleijenberg G.	Afd. Medische Psychologie, Academisch Ziekenhuis St Radboud, Nijmegen.	[Chronic fatigue syndrome. II. Psychosocial hypothesis]. [article in Dutch]	Ned Tijdschr Geneeskd 1991 Oct 26;135(43):2010-4	
Wachsmuth JR, MacMillan HL.	Department of Psychiatry, Hospital for Sick Children, Toronto, Ontario, Canada.	Effective treatment for an adolescent with chronic fatigue syndrome.	Clin Pediatr (Phila) 1991 Aug;30(8):488-90	
Wemm KM Jr, Trestman RL.		The effects of a laboratory stressor on natural killer cell function in chronic fatigue syndrome patients.	Psychosomatics 1991 Fall;32(4):470-1	
Wessely S. Review Review, Tutorial		Chronic fatigue syndrome.	J Neurol Neurosurg Psychiatry 1991 Aug;54(8):669-71 comment in: J Neurol Neurosurg Psychiatry. 1992 Jan;55(1):85	
Wood GC, Bentall RP, Gopfert M, Edwards RH.	Department of Medicine, Royal Liverpool Hospital.	A comparative psychiatric assessment of patients with chronic fatigue syndrome and muscle disease.	Psychol Med 1991 Aug;21(3):619-28	The psychiatric status of patients with chronic fatigue syndrome (N = 34) and muscle disease (N = 24) attending a general medical clinic was studied. Among fatigue patients 14 (41.2%) were cases and a further 9 (26.5%) were subcases of psychiatric disorder as defined by CATEGO. A variety of diagnoses was found. Significantly fewer of the muscle patients had a psychiatric disorder with 3 (12.5%) being cases and 1 (4%) a subcase. The relative risk of psychiatric disorder in patients with chronic fatigue syndrome compared to patients with muscle disease was 3.3:1.
Woods TO, Goldberg DP.	Mental Illness Research Unit, University of Manchester, UK.	Psychiatric perspectives: an overview.	Br Med Bull 1991 Oct;47(4):908-18	This chapter reviews the evidence concerning the importance of psychological and social factors in the aetiology and pathogenesis of chronic fatigue syndrome. The diagnosis is often offered to doctors by patients; and we consider attribution, stigma, collusion between doctor and patient, and abnormal

				illness behaviour in this context. We then give a brief description of a model for common mental disorders, and show how chronic fatigue syndrome relates to this model. It emerges that there are special vulnerability factors in these patients' personalities before the viral illness, but the disorder is seen as being released by the viral illness. By the time the disorder becomes established the original causal nexus is seen as no longer so important, and the disorder can be seen as a form of abnormal illness behaviour maintained by special factors. The implications for treatment are then considered.
Wylie B.		Muscle versus brain: chronic fatigue syndrome.	Med J Aust 1991 Feb 4;154(3):220 comment on: Med J Aust. 1990 Nov 5;153(9):530-4	
Wysenbeek AJ, Shapira Y, Leibovici L.	Department of Medicine B, Beilinson Medical Center, Petah Tiqva, Israel.	Primary fibromyalgia and the chronic fatigue syndrome.	Rheumatol Int 1991;10(6):227-9	Thirty-three primary fibromyalgia patients were investigated for chronic fatigue syndrome symptoms. Significant fatigue was reported by 21/33 patients (63.6%), and patients reported various flulike symptoms, yet only 7/33 patients (21.2%) fulfilled criteria for the chronic fatigue syndrome. Only one patient reported painful lymph glands and four patients reported fever. Thus, symptoms of painful glands or fever might serve as clinical indicators, distinguishing between fibromyalgia and the chronic fatigue syndrome.
Yeomans JD, Conway SP.	Department of Psychiatry, St Jame's University Hospital, Leeds, U.K.	Biopsychosocial aspects of chronic fatigue syndrome (myalgic encephalomyelitis).	J Infect 1991 Nov;23(3):263-9	Fifteen patients, with a primary complaint of chronic fatigue, were referred to a physician by their general practitioners. Psychological distress, measured by simple psychiatric rating scales was common, but specific psychiatric diagnoses, derived from a comprehensive diagnostic interview, occurred less frequently. One questionnaire (Montgomery-Asberg depression rating scale) found emotional distress in 93%, but the diagnostic instrument (Present State Examination) suggested depressive syndromes in only two patients (13%). There were significant occupational difficulties in 87%. No consistently abnormal indices of biochemical or immunological function were found, nor evidence of acute or chronic infection. Chronic fatigue syndrome (CFS) is associated with physical, psychological and social distress. The illness cannot be defined using just one of these dimensions. Such a unilateral approach has resulted in unnecessary controversy over the nature of the 'real' core of CFS. A problem-oriented approach, recognising the multi-factorial and overlapping cause and effect issues in CFS, may be of more benefit to patients.