

Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome

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Background: Chronic fatigue syndrome (CFS) is a disorder of unknown etiology, consisting of prolonged, debilitating fatigue, and a multitude of symptoms including neurocognitive dysfunction, flu-like symptoms, myalgia, weakness, arthralgia, low-grade fever, sore throat, headache, sleep disturbances, and swelling and tenderness of lymph nodes. No effective treatment for CFS is known.

Objective: The purpose of the study was to evaluate the efficacy of the reduced form of nicotinamide adenine dinucleotide (NADH) ie, ENADA© the stabilized oral absorbable form, in a randomized, double-blind, placebo-controlled crossover study in patients with CFS. Nicotinamide adenine dinucleotide is known to trigger energy production through ATP generation which may form the basis of its potential effects.

Methods: Twenty-six eligible patients who fulfilled the Center for Disease Control and Prevention criteria for CFS completed the study. Medical history, physical examination, laboratory studies, and questionnaire were obtained at baseline, 4, 8, and 12 weeks. Subjects were randomly assigned to receive either 10 mg of NADH or placebo for a 4-week period. Following a 4-week washout period, subjects were crossed to the alternate regimen for a final 4-week period.

Results: No severe adverse effects were observed related to the study drug. Within this cohort of 26 patients, 8 of 26 (31%) responded favorably to NADH in contrast to 2 of 26 (8%) to placebo. Based upon these encouraging results we have decided to conduct an open-label study in a larger cohort of patients.

Conclusion: Collectively, the results of this pilot study indicate that NADH may be a valuable adjunctive therapy in the management of the chronic fatigue syndrome and suggest that further clinical trials be performed to establish its efficacy in this clinically perplexing disorder.

Ann Allergy Asthma Immunol 1999;82:185- 191.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a poorly understood disorder of unknown etiology,¹ with a reported prevalence of up to 3/1000 population.²⁻⁴

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This work was supported by a grant from Birkmayer Pharmaceuticals.

Received for publication August 1, 1998.

Accepted for publication in revised form November 28, 1998.

The commonly encountered features in patients with CFS are fatigue, impairments in concentration and short term memory, musculoskeletal pain and sleep disorders.⁵⁻⁸ The syndrome is characterized by profound, debilitating fatigue lasting at least 6 months often beginning abruptly after a viral infection and not meeting the criteria for other medical or psychiatric disorders, and is characteristically worse following levels of physical exertion that had been easily tolerated in the past and a combination of other prominent symptoms. The Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia have defined criteria for the diagnosis of CFS.⁵ The CDC have established that unexplained, debilitating fatigue of at least 6 months duration must be present along with four or more of the following symptoms including neurocognitive dysfunction, myalgias, sore throats, headaches, postexertional malaise, joint pain, sleep disturbances, or swelling and tenderness of lymph nodes. Chronic fatigue syndrome is therefore a clinically defined condition but there are no definitive laboratory parameters available for diagnosis made solely upon clinical symptomatology and exclusion of other diseases associated with fatigue. Symptoms can vary in intensity and frequency, and often a cyclic pattern is exhibited. Relapses or worsening of symptoms are common and duration of symptoms vary in individual cases. The disorder is more recognized in affluent cultures and is more prevalent in Caucasian females with an age predominant distribution between 30 to 50 years. The pathophysiology is unclear and there presently is no known consistently effective or generally accepted treatment for CFS.

Despite the dearth of knowledge concerning the cause of CFS, it is generally accepted that there may be a dysfunction of the neurocrine-endocrinologic-immunologic (NEI) network in CFS and several theories have focused on each of the three limbs of the NEI network. One theory suggests that the syndrome results from a dysfunction of the immune system and several subtle immunologic abnormalities have been described in patients with CFS.⁹⁻¹² These include low levels of specific immunoglobulins reported in 17% to 71% of cases,^{13,14} the presence of circulating immune complexes in over 50% of patients, and increased ratios of CD4/CD8 T-lymphocytes. **11,11** Other abnormalities of the immune system included a decrease in natural killer (NK) cells⁹⁻¹⁰ which appear to play a major protective role in viral infection. A second theory emphasizes the role of neurally mediated hypotension (NHM). Studies utilizing a 3-stage tilt table test have shown an abnormal response in patients with CFS compared with controls and demonstrate an uncompensated NHM which is thought to be the cause of the fatigue.¹⁷ A third, but not mutually exclusive theory, is one that suggests metabolic dysfunction owing to stress, viral infection,¹⁸⁻²¹ allergic disease or a host of other factors.²² Patients with CFS have increased 2'-5' A synthetase and RNase L activity.^{23,24} This in turn leads to a depletion of cellular ATP that may be the pivotal metabolic lesion responsible for severe fatigue, cognitive disturbances, and other manifestations of the syndrome. Since stress, allergy, and infections may either trigger or exacerbate the clinical course, control of these factors is critical in the management of patients with CFS.²⁵ Nicotinamide adenine dinucleotide (NADH), the coenzyme, is known to trigger energy production through ATP generation.²⁶⁻²⁸ This knowledge has provided the rationale for the present study.²⁹ It consists of the ability of the coenzyme to replenish depleted cellular stores of ATP, thus improving the fatigue and cognitive dysfunction characteristic of the disorder.

The purpose of the present study was to evaluate the efficacy of the reduced form of NADH administered orally to a group of patients with CFS in a double-blind, placebo-controlled crossover study.

MATERIALS AND METHODS

Entry Criteria

Patients fulfilling the CDC criteria for CFS were referred by a variety of physicians, self-referred or recruited from the Division of Allergy-Immunology

of the Department of Pediatrics at Georgetown University Medical Center, Washington, DC. A standardized 50-question screening questionnaire was developed for use in all subjects to determine and consider patient eligibility and therapeutic outcome. Following initial assessment of the severity of fatigue and symptoms by a screening questionnaire, detailed telephone interviews were conducted by a physician with potential candidates. Before commencement of the study, approval was obtained from the Georgetown University Institutional Review Board and written informed consent was obtained from each subject prior to entry into the study. Subjects ranging from 20 to 70 years of age who met the CDC criteria for CFS were eligible for enrollment.⁵ Inclusionary criteria included at least 4 symptoms such as: mild fever or chills, sore throat, painful adenopathy (posterior or anterior cervical or axillary),

generalized muscle weakness, myalgias, prolonged generalized fatigue after previously tolerated levels of physical activity, migratory arthralgias without swelling or redness, neuropsychologic complaints, sleep disturbances, and two physical signs, including low grade fever, nonexudative pharyngitis, palpable or tender anterior or posterior cervical lymph nodes. Subjects were allowed to continue taking currently used medications. Medications used 6 months prior to the study and during the study were recorded as concomitant medications.

Exclusionary Criteria

Subjects with fatigue that could be explained by the presence of other evident medical or psychiatric illness, with current psychotic and bipolar disorders, current substance or alcohol dependence, pre-existing and ongoing depression at the time of onset of the chronic fatigue were excluded from the study. Patients with a history of established medical conditions that could be contributing to fatigue, such as, hepatitis, untreated hypothyroidism, psychiatric illness, cancer, AIDS, severe

anemia, multiple sclerosis, Lyme's disease and autoimmune diseases such as lupus were excluded. The use of antidepressants, lithium, neuroleptics, and monoamine inhibitors were generally considered exclusionary criteria.

Study Design

The study design [FDA approved (IND #49,635)] consisted of a randomized, double-blind, placebo-controlled crossover protocol. A thorough medical history, physical examination, laboratory studies, and completion of a questionnaire on the severity of fatigue and symptoms was performed at baseline, week 4, week 8 and week 12. Subjects were randomly assigned at week 0 to receive NADH or placebo for a 4-week period. At week 4, a 4-week wash-out period was begun in which no study drug was given. At week 8, a final 4-week period commenced in which subjects were crossed over to the alternate regimen. Subjects were monitored for toxicity throughout the study period with appropriate laboratory testing. The subjects were asked to report all symptoms that occurred during the treatment regimen, and all symptoms that did not occur at baseline were recorded as adverse experiences. Included in the physical assessment were the following: blood pressure, body weight and temperature, and hand dynamometry measurements as a test of strength and endurance. Peripheral venous blood and urine samples were also obtained from each participant for the measurement of hematologic, biochemical, and immunologic parameters.

Laboratory Assessment

Laboratory studies were performed at laboratories at Georgetown University Medical Center (Washington, DC) and at Birkmayer Laboratories (Vienna, Austria). The following laboratory studies were performed: a complete blood count with differential white blood cell count, erythrocyte sedimentation rate, a panel of 20 serum chemistry tests, urinalysis, serum quantitative immunoglobulin concentrations (IgG, IgM, IgA, and IgE), enumeration and quantitation of lymphocyte subsets (CD3, CD4, CD8, CD19, and CD16/56), and oxidoreductase enzyme assay. Baseline serologic titers of EBV, including early antigen (EA), nuclear antigen (NA) and IgG and IgM to EBV capsid antigen (anti VCA), screening thyroid function levels including T4 and thyroid stimulating hormone levels (TSH), serum antibody titers to human herpesvirus 6 (HHV-6), HIV, rheumatoid factor, and hepatitis B and C (HBS Ag, anti-HCV) were done. During the screening process, three cases of hepatitis C and one case of hypothyroidism were detected with laboratory blood studies. Data and statistical analysis were conducted by Birkmayer Pharmaceuticals (Vienna, Austria) and Georgetown University Medical Center (Washington, DC). The data were also submitted to an independent auditor to confirm and validate the findings.

Symptom Scoring System

The assessment of clinical well-being and severity of symptoms was assessed using a \pm 50-item questionnaire that was developed by our staff, utilizing the currently accepted CDC criteria for CFS.¹ Topics included fatigue, memory and concentration difficulties, muscle aches, muscle weakness, joint aches, lymphadenopathy, headaches, sore throat, sleep disturbance, mood changes, and other related symptoms. Each item in the questionnaire was assessed on a scale from 1 to 4 where 1 represented the minimum severity and 4 the maximum severity of symptoms (1 = none of the time, 2 = some of the time, 3 = most of the time, and 4 = all of the time). Subjects also evaluated how they were

feeling on the day of evaluation. A cumulative score was calculated with a range from 50 to 200, with 200 indicating the maximum and 50 the minimum score. Follow-up questionnaires were completed at monthly intervals upon each visit. An arbitrary symptom scoring system was developed according to the following formulation:

$$\begin{aligned} \text{Symptom score} &= \frac{\text{subject score} - \text{minimum score}}{\text{maximum score} - \text{minimum score}} \\ &= \frac{\text{subject score} - 50}{200 - 50} \\ &= \frac{\text{subject score} - 50}{150} \end{aligned}$$

Statistical Assumptions and Analyses

External validation studies were conducted with normal healthy subjects and indicated a statistically significant difference when compared with patients with chronic fatigue syndrome. Average mean symptom scores for normals ranged from 0.01 to 0.13 in contrast to patients with chronic fatigue syndrome whose scores ranged from 10.9 to 55.8 ($P < .001$).

An analysis of reproducibility was determined when the questionnaire was given to the same subjects repeatedly. Treating the data as a repeated measures analysis (repeated measures on the same test subject), the null hypothesis is that $t_1 = A_2 = I_3 = A_4$; that is, there is no difference in response among the four times (week 0, week 4, week 8, and week 12). The repeated measures analysis of variance gives a $P < .001$. Graphic analysis of residuals shows that the residuals are approximately distributed; that is, there is not a systematic variation among the four column means and it is appropriate to conclude that there is a difference in response among the weeks. Using a multiple comparison test to examine the differences between mean responses two at a time, there is no significant difference between week 1 versus week 2, week 1 versus week 3, or week 2 versus week 3. Week 0 is significantly different from all the others.

An individual was considered improved if s/he demonstrated at least a 10% improvement. The degree of improvement for the results to show a positive effect was an improvement by one point in 10 questions or by 2 points in 5 questions.

Analysis of Data

Data were analyzed using a test of difference between two proportions.

$$z = \frac{(\hat{p}_1 - \hat{p}_2) - (P_1 - P_2)}{\sqrt{\frac{\bar{p}(1 - \bar{p})}{n_1} + \frac{\bar{p}(1 - \bar{p})}{n_2}}}$$

$$\bar{p} = \frac{x_1 + x_2}{n_1 + n_2}$$

Drug Administration

Subjects were randomly assigned to either treatment or placebo groups and patient numbering occurred in the sequence of subject enrollment. Subjects were given 10 mg of NADH, ie, ENADA8, the stabilized, oral absorbable reduced NADH or the placebo equivalent (two 5-mg tablet formulation) at week 0. All study drugs were distributed in identically marked study boxes, and the tablets both of identical appearance were contained in blister packs. Subjects

were instructed to take the dosage two 5-mg tablets orally, once a day in the morning about 45 minutes before breakfast on an empty stomach with a glass of water. Subjects received the study drug for a 4-week period.

Compliance Monitoring

Participants also were strictly instructed to keep a diary and drug log throughout the study which was reviewed and monitored upon each visit. The study medication was counted and monitored at week 4 and week 12 and returned to the manufacturer for further evaluation and the patient compliance and adherence was evaluated at each visit.

RESULTS

Of the 35 subjects initially-enrolled, 33 were able to complete the study and two dropped out due to non-compliance. Of the 33, 9 who were receiving psychotropic drugs were dropped from the study analysis leaving a total of 26 subjects available for analysis.

Shown in Table I are the demographic characteristics of the study population. Of the 26 evaluable subjects, 17 (65%) were females and 9 (35%) males. The subjects ranged from 26 to 57 years of age (mean 39.6 years) and had fatigue for a duration of 1 to 16 years (mean 7.2 years). Twenty-five patients were Caucasian and one patient was Afro-American. The presenting clinical symptoms in the study population are shown in Table 2. It can be seen that fatigue, neurocognitive difficulties, and sleep disturbances were present in all patients. Postexertional malaise, headache, and muscle weakness likewise represented high frequency symptomatology and the remainder had decreasing frequency of myalgias, arthralgias, and lymphadenopathy. Shown in Table 3 is a representative sample of questions from the questionnaire.

Table 1. Demographic Characteristics of the Study Population

Demographics	
Female:male	17:9
Age	26-57 years (mean 39.6 years)
Mean duration of fatigue	1-16 years (mean 7.2 years)
Race, Caucasian:Afro-American	25:1

No detectable abnormalities were noted in the serum immunoglobulin concentrations or lymphocyte subset analysis in any of the subjects at baseline or after treatment and further immunologic testing was discontinued after the first group of patients. No correlation between immune function or clinical status nor treatment response could be established. No differences in oxidoreductase activity were observed before or after NADH treatments.

Table 2. Clinical Symptoms Presenting in Subjects

Symptom	Number of Patients (%) n = 26
Fatigue	26 (100)
Neurocognitive difficulties	26 (100)
Sleep disturbance	26 (100)
Postexertional malaise	25 (96)
Headaches	24 (92)
Muscle weakness	24 (92)
Arthralgia	22 (85)
Myalgias	21 (81)
History of allergy	21 (81)
Swelling and tenderness of lymph nodes	18 (69)

The results of the EBV serologic titers. in the first group of 15 revealed that 9/15 (60%) subjects had EBV-EA >40. Results are shown in Table 4. There were 6/15 (40%) subjects who had HHV-6 titers = 1: 160, suggesting current or

recent infection. One of 26 subjects was anti-HCV positive. A history of allergies was reported in 21/26 (81%) subjects. All subjects tested were HIV negative and the rheumatoid factor (RF) was negative. Elevated levels of IgE were detected in 2/15 (13%) subjects. T4 and TSH levels were within normal limits for all subjects.

Clinical Outcomes

Although clinical and laboratory measurements were made as parameters of clinical outcome, the results showing efficacy came primarily from the subjective criteria of the questionnaire. The results of the outcomes were the symptom scoring system, the results of which are shown in Table 5. Using the arbitrary scoring system, 8/26 (31%) subjects showed = 10% improvement while on the study drug in contrast to 2/26 (8%) who received placebo. Assuming that these improvements came from two independent samples of subjects, the success rate **for the drug** is 31 % and for the placebo 8% ($P < .05$).

Using a self-evaluated questionnaire, 9/26 (35%) subjects were able to correctly evaluate the treatment period they were on NADH. Further, 18 of 25 (72%) study patients thus far enrolled in a longer open label follow-up study reported significant improvement in clinical symptomatology and energy levels.

No severe adverse effects were observed related to the study drug. The related adverse events noted were single cases of being overly stimulated, mild loss of appetite, heartburn, in

creased incidence of gas and an odd taste and dryness reported 011 the first day of taking the drug. These events were mild enough that the subjects were able to continue taking the drug without problem. No interference was observed between NADH and other concomitant medications taken during the study investigational period.

Blood pressure and hand dynamometry were measured throughout the study with no significant difference noted. Patients with hypertension (1/26), hypotension (2/26), and normotensives in our study did not show any decrease in blood pressure values following NADH administration. Laboratory testing also included the measurement of plasma neurotransmitter concentrations and the urinary concentrations of serotonin metabolites, ie, 5-hydroxyindole acetic acid (5-HIAA). The urinary concentrations of 5-HIAA were elevated prior to treatment in 50% of patients ($P < .05$). Following NADH treatment, these elevated 5-HIAA concentrations returned to the normal range. The urinary concentrations of the serotonin metabolite (5HIAA) were measured by high performance liquid chromatography. The interassay and intraassay precision ranged from 3.0% to 6.5% and from 2.5% to 5.8%, respectively using a method developed by Birkmayer Laboratories.

DISCUSSION

The results of the present study show a beneficial effect of NADH in the amelioration of the symptom score seen in patients compared with control subjects. Four times as many patients responded to NADH in contrast to placebo. This response was characterized by improvement in fatigue, decrease of symptoms, and improvement in quality of life.

In these preliminary studies, although we employed a dosage of 10 mg of NADH per day, it should be emphasized that different patients may have different needs. The reported feeling of one subject being overly stimulated, suggests that the dosage could be decreased. Other non-responding patients in contrast may require an increased dosage. In the present study modification of dosage: was not made on the basis of weight.

. Although the duration of the study was 12 weeks, subjects received NADH for only 4 of the 12 weeks. Perhaps a longer period of treatment might enhance the beneficial effects of NADH and could be reflected in a more beneficial and protracted response. This could be evaluated in a longer term open-label follow-up study which is currently being planned.

An additional important outcome of the study was the finding that 3 of the initial 35 screened subjects (3/35) were found to be seropositive for hepatitis C virus. This observation not only highlights the importance of this viral infection as a cause of fatigue, but also underscores the need for the clinician to consider this in the diagnostic approach of the patient who presents with fatigue. Our immunologic studies reveal no abnormalities of immune

function before or after NADH administration. One should consider, however, that at the particular time of clinical evaluation and blood drawing there may not have been an exacerbation of the disease.

Table 3. Sample Questions from CFS Symptom Questionnaire

Since Your Last Visit	None of the Time	Some of the Time	Most of the Time	All of the Time	Today
1. Have you had extreme fatigue?	1	2	3	4	5
2. Was it made worse with exercise?	1	2	3	4	5
3. Does your fatigue limit your daily activity?	1	2	3	4	5
4. Have you felt like you had a fever or chills?	1	2	3	4	5
5. Have you had a sore throat?	1	2	3	4	5
6. Have your neck glands felt swollen?	1	2	3	4	5
7. Have the glands under your arms felt swollen?	1	2	3	4	5
8. Have your muscles felt weak?	1	2	3	4	5
9. Have your muscles ached?	1	2	3	4	5
10. Have you felt sick after doing something strenuous?	1	2	3	4	5

Table 4. Results of EBV-EA and HHV-6 Viral Serology

	<1:40	>1:40	<1:160	>1:160
EBV-EA	6/15 (40%)	9/15 (60%)	N/A	N/A
HHV-6	N/A	N/A	9/15 (60%)	6/15 (40%)

N/A = not applicable.

Table 5. Clinical Outcomes (%) Using Subject Symptom Scoring System

Patient	Week 0	Week 4	Week 8	Week 12
1	51.7	51.7	51.7	51.7
2	24.5	10.9	17.0	29.3
3	42.2	46.3	44.9	42.9
4	37.4	29.9	27.2	37.4
5	55.8	57.1	48.4	34.7
6	24.8	14.4	30.7	33.3
7	48.3	32.7	42.9	49.0
8	55.8	29.9	41.5	32.7
9	28.6	27.2	23.1	24.5
10	27.2	22.2	31.4	31.3
11	31.3	28.6	28.6	32.7
12	28.1	23.8	34.0	32.7
13	43.5	39.5	27.9	32.0
14	40.1	30.6	22.5	21.1
15	42.2	38.8	39.5	35.4
16	20.9	29.4	22.8	14.4
17	28.1	22.8	16.9	9.8
18	22.2	28.1	20.3	23.5
19	55.6	45.1	38.6	33.3
20	26.8	25.5	28.1	26.1
21	31.4	18.9	20.3	17.6
22	22.2	24.2	31.3	10.5
23	35.3	21.6	26.8	26.8
24	41.8	34.6	33.3	39.2
25	24.2	17.6	20.9	16.3
26	40.5	28.7	30.1	31.4

Although no significant changes were detected in blood pressure in the present study, other preliminary studies performed in our laboratories have suggested that NADH may cause a decrease in blood pressure in hypertensive rats (SHR).³⁰ We, however, did not observe this effect in human subjects who for the most part were normotensive. The

lowering of blood pressure by NADH would have been an undesirable outcome particularly in hypotensive or NMH patients but our study showed no evidence that blood pressure was affected.

Stress, allergy, and infections appear to be critically involved in the pathogenesis or exacerbation of CFS. The involvement of the serotonergic and noradrenergic pathways appears to be disrupted in patients with CFS. Perturbations have been demonstrated in the metabolism of the 5-hydroxyindole acetic acid, 5-hydroxytryptamine, and prolactin.¹¹ Measuring the urinary concentration of 5-HLAA may serve not only as a diagnostic aid for CFS but also be a predictive marker of physical and psychological dysfunction occurring in patients with CFS.

The finding of a high incidence of allergies (21/26) was observed in our study group is significant since it is known that a worsening of the disease often can be attributed to untreated allergic disease.²⁵ Allergists/immunologists therefore are perhaps the best suited physicians to diagnose and manage patients with CFS, since the pathogenesis involves immune dysfunction and the interplay of other environmental factors and the careful management of allergic disease can lead to a striking improvement, and therefore are uniquely poised to evaluate and manage patients with CFS. The use of NADH may thus be a valuable adjunctive therapy in the management of CFS and the results of the present study suggest that further clinical trials be performed to establish its efficacy in this clinically perplexing disorder.

ACKNOWLEDGMENT

The authors would like to express their sincere gratitude MaryLu Halperin, RN, MPH for her indefatigable efforts in monitoring the study.

REFERENCES

1. Straus SE. History of chronic fatigue syndrome. *Rev Infect Dis* 1991;13 (suppl 1):S2-7.
2. Lloyd AR, Hickie I, Boughton CR, et al. Prevalence of chronic fatigue syndrome in an Australian population. *Med J Aust* 1990;153:522-528.
3. Bates DW, Schmitt W, Buchwald D, et al. Prevalence of fatigue and chronic fatigue syndrome in primary care practice. *Arch Intern Med* 1993;153: 2759-2765.
4. Buchwald D, Umali P, Umali D, et al. Chronic fatigue and the chronic fatigue syndrome: prevalence in a Pacific Northwest Health Care System. *Ann Intern Med* 1995;123:81-88.
5. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994;121: 953-959.
6. Komaroff AL, Buchwald DS. Chronic fatigue syndrome: an update. *Annu; Rev Med* 1998;49:1-13.
7. Sharpe MC, Archard LC, Banatvala JE, et al. A report-chronic fatigue syndrome: guidelines for research. *I R Soc Med* 1991;84:118-12L
8. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med* 1988;108:387-398.
9. Buchwald D, Komaroff AL. Review laboratory findings for patients chronic fatigue syndrome. *Rev Infect Dis* 1991,13 (suppl):S]2-18.
10. Lloyd AR, Wakefield D, Boughton CR, Dwyer JM. Immunological abnormalities in the chronic fatigue syndrome. *Med J Aust* 1989;151: 122-124.
11. Klimas NG, Fernando FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbiol* 1990;28:1403-1410.
12. Mawle AC, Nisenbaurn R, Dobbins JG, et al. Immune responses associated with chronic fatigue syndrome: a casecontrolled study. *J Infect Dis* 1997; 136-141.
13. Lloyd A, Hickie I, Wakefield D, et al. A double-blind, placebo-controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome. *Amer J Med* 1990;89: 562-568.
14. Peterson PK, Shepard J, Macres M, et al. A controlled trial of intravenous G in chronic fatigue syndrome. *Amer J Med* 1990;89:554-560.
15. Lloyd A, Hickie I, Hickie C, et al. Cell-mediated immunity in patients with chronic fatigue syndrome, healthy control subjects and patients with major depression. *Clin Exp Immunol* 1992;87:76-79.

16. Peakman M, Deale A, Field R, et al. Clinical improvements in chronic fatigue syndrome is not associated with lymphocyte subsets of function or activation. *Clin Immunopathol* 1997;82: 83-91.
17. Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA* 1995;274:961-967.
18. Sumaya CV. Serological and virologic epidemiology of Epstein-Barr virus: relevance to chronic fatigue syndrome. *Rev Infect Dis* 1991;13 (suppl): S19-25.
19. Straus SE, Dale JK, Tobi M, et al. Acyclovir treatment of the chronic fatigue syndrome. lack of efficacy in a placebo-controlled trial. *N Engl J Med* 1988;319:1692-1698.
20. See DM, Tilles JG. Alpha interferon treatment of patients with chronic fatigue syndrome. *Immunol Invest* 1996; 25:153-164.
21. Brook MG, Bannister BA, Weir WRC. Interferon-alpha therapy for patients with chronic fatigue syndrome [Letter]. *J Infect Dis* 1993; 168:791-792.
22. Bellanti JA, Forsyth LM, MacDowell AL, Preuss HG. Chronic fatigue syndrome (CFS): unraveling a new dilemma. *J Am College Nutr* 1998 (in press).
23. Sudadolknik RJ, Reichenbach NK, Hitzges P, et al. Upregulation of the 2-5 A synthetase/RNase L antiviral pathway associated with chronic fatigue syndrome. *Clin Infect Dis* 1994;18 (suppl):S96-104.
24. Sudadolknik RJ, Peterson DL, O'Brien K, et al. Biochemical evidence for a novel low molecular weight 2-5 A dependent RNase L in chronic fatigue syndrome. *Interferon Res* 1997;17: 377-385.
25. Straus SE, Dale JK, Wright R, Metcalfe DD. Allergy and the chronic fatigue syndrome. *J Allergy Immunol* 1988;81:791-795.
26. Birkmayer JGD, Vrecko C, Vole D, Birkmayer W. Nicotinamide adenine dinucleotide (NADH)-new therapeutic approach to Parkinson's disease, comparison of oral and parenteral application. *Acta Neurol Scand* 1993;87 Suppl 146:32-35.
27. Birkmayer JGD. Coenzyme nicotinamide adenine dinucleotide, new therapeutic approach for improving dementia of the Alzheimer type. *Ann Clin Lab Sci* 1996;26:1-9.
28. Birkmayer JD, Birkmayer W. The coenzyme nicotinamide adenine dinucleotide (NADH) as biological antidepressive agent experience with 205 patients. *New Trend in Clin Neuropharm* 1991;5:75- 86.
29. Bellanti JA, Forsyth LM, MacDowell-Carneiro AL, Birkmayer GD, Preuss HG. NADH and chronic fatigue syndrome (CFS): a new therapeutic approach [Abstract]. *Ann Allergy Asthma Immunol* 1998; 80:82.
30. Bushehri N, Jarrell ST, Lieberman S, et al. Oral reduced b-nicotinamide adenine dinucleotide (NADH) and lipid profile in hypertensive rats (SHR). *J Geriatric Nephrol* 1998; (in press).
31. Bakheit A.MO, Behan PO, Dinan TG, et al. Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. *Br Med J* 1992;304:1010-1012.
32. Forsyth LM, MacDowell-Carneiro AL, Birkmayer GD, et al. The measurement of 5-HIAA urinary concentrations as a predictive marker of efficacy of NADH in chronic fatigue syndrome (manuscript in preparation) 1998.

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Printed in the U.S.A.

VOLUME 82, FEBRUARY, 1999