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EFFECTIVE TREATMENT OF SEVERE CHRONIC FATIGUE: A REPORT OF A SERIES OF 64 PATIENTS

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ABSTRACT. Objectives: To determine the underlying causes of severe chronic fatigue states and the effect of concurrently treating the underlying etiologies.

Methods: Sixty-four patients with a median of three years of severe fatigue, which markedly limited their activity, were studied. These patients were characterized by a mix of symptoms including recurrent sore throats, swollen glands, increased thirst, sleeplessness, achiness, and poor memory and concentration without apparent cause. They presented in our office during 1991–1993 and were selected by consecutive sampling. The patients were assessed and treated for the processes noted below.

As fatigue is purely subjective, the patient determined if they showed worsening, no significant change, significant but incomplete improvement, or much improvement [that is, fatigue no longer a problem].

Results: 46 patients had at least three or more contributing problems. Fibromyalgia was present in 44 patients. Overt or subclinical hypothyroidism and hypoadrenalism were suspected in thirty and 40 patients respectively. Superinfections associated with immune dysfunction [e.g., bowel parasites or yeast overgrowth] were suspected in thirty cases. Improvement with micronutrient supplementation was noted.

Depression, anxiety/hyperventilation and situational stresses were considered to be the primary processes in four, four, and three patients respectively.

Treatment resulted in complete resolution of fatigue in 57 percent and significant but incomplete improvement in 39 percent of the patients. Improvement was seen at a median time of seven weeks.

Conclusions: Severe chronic fatigue states are multifactorial processes that, in many patients, respond well to treatment.

KEYWORDS. Fatigue, fibromyalgia, adrenal insufficiency, hypothyroidism, chronic fatigue syndrome

INTRODUCTION

Severe chronic fatigue states [SCFS] are common. Chronic fatigue syndrome [CFS], representing a small subset of SCFS, is rare. A recent report by Price et al.[1] suggests that only one in 13,535 people [or approximately 20,000 patients in the United States] meet strict Center for Disease Control [CDC] criteria for CFS. By CDC estimates, the prevalence is even lower, at 2 to 7 per 100,000.[2] The prevalence of persistent, often disabling, fatigue has been estimated to be much higher-often up to six million patients for fibromyalgia alone.[3] Unfortunately, despite having sought help for many years, people suffering from severe fatigue often receive little benefit from treatment. This paper reports on an approach to the evaluation and treatment of severe chronic fatigue states which we have found to be effective.

A key factor in helping patients with chronic fatigue was the realization that a combination of interrelated problems was usually occurring. Patients often improved dramatically and quickly when all the underlying problems were treated simultaneously. If only one problem was treated, or if the problems were not treated simultaneously, often the patient's improvement was only partial. In our current study, we examined sixty-four patients with chronic and severe fatigue to define the multiple underlying causes and to assess the efficacy of treating all the discovered problems.

MATERIALS AND METHODS

The study population consisted of fifty-six females and eight males, ages twenty to seventy-seven years [average age forty-five years] whose major complaint was severe

chronic fatigue of at least two month's duration which the patients felt significantly limited their activity. These patients were characterized by a mix of symptoms including recurrent upper respiratory infections [URls], sore throats, swollen glands, increased thirst, achiness, poor sleep, and poor memory and concentration. We defined these patients as having a severe chronic fatigue state.

These patients presented in our office from 1991 to 1993. Most of these patients had been through numerous evaluations and/or treatments without relief before entering our trial. The median duration of their fatigue was three years (average two years; range two months twenty-five years). Patients were given a thorough history and physical examination. Complete blood count (CBC), automated chemistry profile (Chem 19), erythrocyte sedimentation rate (ESR), urinalysis (UA), B_{12}, serum iron, total iron binding capacity (TIBC), ferritin, glycosylated hemoglobin, thyroid functions and cortrosyn stimulation testing were done. In refractory cases, we checked for stool ova/parasites [O&P], giardia and cryptosporidium [tested in nineteen patients]. Special attention was given to checking for:

1. Subclinical hypothyroidism—for the reasons noted in the discussion, if the free thyroxine (FT_4) index was low normal and signs and symptoms suggestive of hypothyroidism were present (for example, constipation, cold intolerance, low temperature, delayed ankle tendon relaxation phase, and so on), a low-dose Synthroid trial (25 to 50 micrograms) was considered (especially if fibromyalgia was present). If the thyroid stimulating hormone (TSH) was over 4 or less than 0.8 (with a low normal FT_4 index), this also weighed in favor of treatment. The free FT_4 and ultrasensitive TSH assays are microparticle enzyme immunoassays for the quantitative determination of free thyroxine and human thyroid stimulating hormone in human serum as measured on Abbotts IMX.
2. Decreased Adrenal Function—A cortrosyn stimulation test was performed at 8:00 AM. Fasting baseline, thirty- and sixty-minute serum cortisol levels were checked after a 25-unit dose of cortrosyn [ACTH] intramuscularly. The test was considered positive for a low baseline if the cortisol was less than 6 mcg/dL. As our experience grew, we found

patients often benefitted dramatically from treatment even if the baseline was as high as 11 mcg/dL. Therefore, we expanded our definition of low baseline to include patients with cortisol levels of up to 11 mcg/dL. These patients received a trial of treatment if they failed to respond fully to other treatment. If a patient showed low adrenal reserve (that is, not doubling at one hour or not increasing by 7 mcg/dL at one-half hour and 11 mcg/dL by one hour), the patient was also treated. Although Jefferies[4,5] felt that most patients needed qid (four times daily) dosing of Cortef [for example, 5 milligrams of Cortef qid), we found that most of those with low reserve did well with 5 milligrams Cortef po (orally) qam (each morning), and, if needed, 2.5 to 5 milligrams at lunchtime. Those with low baselines were more likely to need 5 to 7.5 milligrams tid (three times daily) or qid. Those who don't respond to lower dosing should receive a trial of qid dosing [giving only 2.5 milligrams qhs (at bedtime)] The cortisol assay is a homogeneous enzyme immunoassay for the quantitation of total cortisol in serum. The reagents are from Cedia Microgenics Corporation and run on the Technicon R.A.

3. Fibromyalgia—Diagnosis was made by the 1990 American College of Rheumatology tender point criteria. Amitriptyline (10 to 50 milligrams), cyclobenzaprine (5 to 20 milligrams), or Trazodone (25 to 75 milligrams) qhs were used to treat disordered sleep in most fibromyalgia patients (see Table 3). We use the terms fibrositis and fibromyalgia interchangeably.

4. Chronic infections:

A. Bacterial—Urinary tract infection (UTI), chronic sinusitis, or other infections were checked for by history and urinalysis. Most of these had been treated by other physicians before the patient's arrival in our office.

B. Bowel parasites—Toward the end of our study, we tested patients refractory to other treatment for bowel parasites. The yield with routine O&P is low even if parasites are present. Because of this we used a purged stool specimen and had the slides read by our lab supervisor and a technologist experienced in looking for stool parasites. Antigen tests for giardia and cryptosporidium were also done. We now test all our chronic fatigue patients for bowel parasites. The objective of the stool purge was to secure a watery, "explosive" sample.[6] We feel

this gives far better reliability than numerous random samples. Patients are instructed to drink 1!/2 ounces of Fleet Phospho-Soda and to collect the watery stool specimens in the three vials containing the preservative sodium acetate-acidic acid-formalin (SAF). We use Meridian Diagnostic Para Pak SAF System and Para Pak Concentration Kit and trichrome stain for differentiation of internal structure of intestinal parasites.

C. Fungal infections—History was taken for risk factors suggestive of possible fungal overgrowth, for example frequent antibiotic use, recurrent vaginal or skin fungal infections, and so on. If this raised a high index of suspicion or the stool microscopic examination was suggestive of fungal overgrowth, a trial of 1 million units of nystatin po qid was given over four to six months. We are currently finding that 200 milligrams of itraconazole (taken with food) po qd (daily) for three to four weeks followed by 100 milligrams qd for one to four months in combination with 500,000 units of nystatin po qid (while on itraconazole) to be more effective. Fluconazole may also be helpful in these patients. Nizoral may aggravate the often subtle adrenal insufficiency frequently seen in patients with chronic fatigue.[7]

5. Depression, anxiety or hyperventilation—These were treated with tricyclic or selective serotonin reuptake inhibitors (SSRIs, for example, Prozac) family of antidepressants if the symptoms were felt to have preceded the fatigue, as opposed to being caused by it. Patients who presented with an ongoing diagnosis of depression without other factors contributing to their fatigue were excluded from the study.

6. Possible micronutrient deficiencies—all patients were placed on a B complex (25 milligrams) vitamin with minerals (such as Berocca Plus or Twin Lab Daily One Caps). Many were placed on two to six tablets of magnesium chloride (Slow Mag) per day (less if diarrhea occurred). Low iron and B_{12} were tested for and treated when present.

We felt that treating coexisting problems simultaneously would improve the effectiveness of treatment. Unfortunately this made it difficult to assess the degree of effectiveness of each individual treatment.

As the patient's symptoms in severe chronic fatigue states are predominately subjective, the determination of degree of improvement after any given treatment was made by the patient. This was complicated, at times, by several treatments being given concurrently.

The experimental nature of parts of the treatment was reviewed with the patient and informed consent was obtained.

RESULTS

As shown in Table 1, thirty-seven of sixty-four patients had almost complete resolution of their fatigue and twenty-five of sixty-four showed significant, but incomplete, improvement. Two out of sixty-four patients had no significant improvement. Improvement was often rapid, at times occurring within a few days. Median length of symptoms before treatment was three years and median time to initial improvement was 1#/4 months (that is, at the first follow-up visit). Patients did at times have temporary exacerbations during their treatment course. Improvement was, however, usually sustained (most patients have remained in follow-up for over one year). Only seven patients had a single underlying contributing diagnosis. Most had three or four underlying problems (see Table 1). Table 2 shows the number of patients felt to have each of the different underlying diagnoses and their response to treatment. Table 3 gives a more detailed breakdown of patient characteristics, contributing diagnoses, and responses to treatment.

Table 1. Clinical Characteristics of the Treatment Group and the Effect of Treatment

Number of patients	64
Male	8
Female	56
Ages	
Range	20–77 years old
Average	45 years old
Duration symptoms present	
Range	2 months to 25 years
Median	3 years
Average	2 years
Time until initial improvement was seen with treatment:	
Range	4 days to 15 months
Average	3 months
Median	1.75 months [that is, first follow-up visit]
Number of contributing diagnoses per patient	Number of patients
1	7
2	11
3	23
4	13
5	9
6	0
7	1
Degree of improvement (out of 64 patients)	Number of patients
Much improved [that is, fatigue no longer a significant problem]	37
Moderate improvement [significant improvement but fatigue is still a problem]	25
No significant improvement	2

Table 2. Number of Patients with Each Suspected Diagnosis and Response to Treatment.

Suspected Diagnosis	Number of Patients	Improved with Treatment	No Clear Improvement with Rx	No Rx or Follow Up
A. Fibromyalgia	44	37	4	3
B. Low Thyroid				
1. By low T_7/high TSH	12	11	1	
2. By symptom/ exam only	18	14	3	1
C. Underactive Adrenal [Hypo-cortisolism]:				
1. Low adrenal baseline [i.e., 8 a.m. Cortisol 0–5.9 mcg/dL]	7	5	2	
2. 8 a.m. Cortisol 6–11 mcg/dL	16	11	3	2
3. Low adrenal reserve	16	15	1	
D. Fungal Overgrowth	23	14	7	2
E. Possible Low B_{12}				
1. <300 PG/ml	7	7		
2. 301-540 PG/ml	19	17	1	1
F. Bowel Parasites: [in 19 pts. checked]				
Cryptosporidium	3	0	3	
Entameba	2	2		
Visceral Larva Migrans	1	1		
Tapeworm	1	1		
G. Depression				
primary	4	4		
secondary	4	4		
Anxiety/hyper-ventilation	4	3	1	

Note: Severe situational stress was felt to be the primary process in 3 patients and a secondary process in 5. Ferritins of 0 to 20 ng/ml and 21 to 40 ng/ml were seen in 7 and 6 patients, respectively. The effect of iron supplementation was not separately monitored.

Table 3. Review of Individual Patient Data

Age	M/F	Hypothyroid Dx/Efct	Hypoadrenal* Dx/Efct	Fibrositis Dx/Efct TR = TRAGER	B_{12} Level pg/ml Efct	Yeast Suspct. DX/Efct
53	M	+ +	8.6 +			
27	F		+ +		348 +	+ No Rx
45	F					
33	F			+ —	540 +	
45	F	+ +	4.8	—	+ No Rx	
40	F	sc +	5.7 ++	+ +	484 +	
47	M		7.6 +	+ + TR		+ — S.E.
42	F	sc +	+ +	+ +		
44	F		7 ++	TR		
44	F					+ +
51	F	sc +	+ ++	+ + TR		
53	F	+ +				
38	F			+ —	270 +	
53	F	+ +		+ + TR		
33	F	sc +		+ — S.E.W. Rx		+ +
37	F	sc +	4.7 +	+ +		+ +
40	F	sc +		+ +	440 +	+ +
50	F	sc +	4 +	+ No Rx		
50				+ + TR	300 +	
59	F					
34	F	+ +	3 —	+ +		+ +
30	F			+ +	294 +	+ +
41	F			+ + TR		
26	M	sc +	+ +	+ +		
55	F		1 ++	+ + TR		
73	F	+ +			220 +	
43	F		+ ++	+ +		
42	F	+ +	+ ±		524 +	+ —
31	F	sc +	11 +	+ +	400 +	+ No Rx
29	F	sc +	8 +	+ No Rx		
21	F	sc ±	+ +	+ + TR		
51	F	sc +	9 +	+ +		+ +
57	F	sc +				

O E & F P C T	Depressed Anxious Hyper- Ventilatory	Ferritin	Symptoms present x mo/yrs	Time until improvement	Much better	Mod. Better	No Sig. chng.
			few months	1 month		+	
			2!/2 years	6 weeks		+	
	work stress		1 year	115 months left	+		
			>1 year	4-6 months	+		
			app. 10 years	1 year	+		
			1 year	7 weeks	+		
			3!/2 years	2!/2 months	+		
	stress		9 months	3 months		+	
	stress		N/A	1 month	+		
			1 year	3 months	+		
			app.4 months	2 months	+		
			2 months	<2 months		+	
	S. L. E.	28	5 years	1 year 2 months with B_{12}		+	
			1!/2 years	2 months		+	
			10 years	weeks	+		
			years	6 weeks	+		
			app. 2–3months	2 months	+		
		29	N/A	6 weeks	+		
			4 years	N/A	+		
			years	without improvement			+
—			>6 years	months	+		
			2 years	1 month		+	
			>4 years	1 month	+		
			3 years	2 months		+	
	HV	23	years intermittent	2 months	+		
	depressed		months	<1 week	+		
			months	1-2 months	+		
		5	8-10 years	4 months		+	
	depressed	20	5 years	2 months		+	
			10 years	4-6 months	+		
			years	4 months		+	
	stress		1!/2 years	N/A		+	
	depressed		years	4 months		+	

Age	M/F	Hypothyroid Dx/Efct		Hypoadrenal* Dx/Efct		Fibrositis Dx/Efct TR = TRAGER		B_{12} Level pg/ml Efct		Yeast Suspct. DX/Efct	
67	F	sc	No Rx	9	No Rx	+	+				
20	F	sc	+	+	+			260	+		
51	F			11	+	+	+	247	+		
33	F	+	+					219	+		
57	F	+	+	+	+	+	+				
48	F			6	-	+	+	359	+	+	—
51	F					+	+	425	No Rx	+	+
40	F					+	+			+	±
39	F					+	+			+	+
49	M			6	—			323	—		
67	M										
58	F			+	++	+	—				
59	M					+	+	513	+	+	+
35	F				TR +	+	+ TR	340	+	+	—
34	F	sc	—	+	+	+	+				
39	F	sc	—	+	+	+	+				
45	F			11	+	+	+				
34	F	+	+			+	+				
45	F			10	++	+	+ TR	425	+	+	+
40	F			2	+			340	+		
74	F					+	+	380	+		
77	M			8	+						
63	M			6	+						
46	F	+	+	+	++			328	+	+	±
44	F					+	+	371	+	+	—
45	F					+	+	387	+		
43	F			10	No Rx	+	++ TR				
42	F	sc	+	+	+	+	+	454	+		
41	F	+	—	+	+					+	+
31	F			+	+	+	+	206	+		
36	F									+	+

*Hypoadrenalism—If based on a low baseline cortisol, the baseline cortisol [in mcg/dl] is noted. A [+] indicates an inadequate adrenal reserve [see Methods]. EFCT = Effect of treatment. A [+] means the patient improved with treatment. A [—] means no improvement with treatment. SC = Subclinical. DX means patient had this diagnosis if [+] is in the column. CS = Cryptosporidium. VLM = Visceral larva migrans. Ferritin is in ng/ml.

O E & F P C T	Depressed Anxious Hyper-Ventilatory	Ferritin	Symptoms present x mo/yrs	Time until improvement	Much better	Mod. Better	No Sig. chng.
			4–5 years	2 months	+		
			months	1–2 months	+		
	depressed	21	>4 years	4 months	+		
		20	1 year	2 months		+	
			years inter.	4 months	+		
	anxious		> 20 years	5 months	+		
CS —	anxious depressed		30years	1 week after Sporanox		+	
			6 years	6 weeks	+		
CS —	depressed		7 years	7 months		+	
	depressed		years	N/A			+
	depressed		6 years	10 months	+		
			many years	2 months	+		
			5–6 years	3 months		+	
			4 years	2 months		+	
			N/A	N/A		+	
			years	2 months		+	
VLM+	stress		1 year	6 weeks		+	
			1-2 years	1 month	+		
		3	9 years	3 months	+		
		26	1!/2 years	2 weeks	+		
Tape Worm			years	months		+	
CS —	stress		4 months	2 months	+		
			1 year	3 months	+		
			8 months	2 months	+		
H.V.		14	2 years	6 weeks		+	
Entmba + +		19	15 years	1 month	+		
			years	1 month	+		
			25 years	2 months	+		
			2 years	1-2 months		+	
Entmba +		46	4 years	4 days	+		
	stress	18	2-3 years	N/A		+	

DISCUSSION

We found that most patients [all but seven] had a combination of at least two underlying problems and forty-six patients had more than two problems. Previous trials have often shown disappointing results when only one underlying cause was sought or treated.

We found that patients—even those with fatigue of over ten years duration—experienced (usually rapid) resolution of their symptoms 57 percent of the time and significant improvement another 39 percent of the time if the multiple underlying problems were identified and treated. Frankly, we were surprised at the degree of improvement shown by our patients.

Why did these patients show such an assortment of problems? The patterns we observed suggested that the primary process might have been hypothalamic dysfunction (caused by viral or other infections) with secondary multiple endocrine (and possibly immune) abnormalities. As Dr. Sternberg notes in her excellent editorial on hypoimmune fatigue states,[8] and Dr. Behan and others note in their studies, hypothalamic-pituitary-adrenal (HPA) axis dysfunction appears to be common in chronic fatigue states.[9,10,11,12,13] This can manifest as borderline or overt adrenal insufficiency and borderline or overt hypothyroidism. In their study on fibromyalgia, Neeck et al.[9] examined baseline and TRH stimulated thyroid function. Although most fibromyalgia patients had normal baseline thyroid functions, their response to TRH stimulation was significantly blunted. The increase of TSH and T_4 after TRH stimulation was approximately 90 percent greater for TSH ($P < 0.05$) and over 800 percent greater for FT_4 ($P < 0.05$) in controls than in fibromyalgia patients. This, combined with a clinical picture suggestive of hypothyroidism, suggests that our current testing misses subtle, but clinically significant, hypothyroidism in these patients. This problem is often accentuated by a low normal TSH [secondary to hypothalamic dysfunction]. The low TSH can further mislead the clinician into thinking thyroid function is adequate. Impairment of receptors for thyroid and adrenal hormones may also impact here. In light of this, an empiric trial of 25 to 50 micrograms of Synthroid a day often resulted in marked improvement. It is suggested that the adrenal insufficiency be treated first. Otherwise, the administration of Synthroid may

accelerate the metabolic breakdown of the patient's cortisol, exacerbating the patient's symptoms. Interestingly, many of our patients exhibited marked polydipsia with normal blood sugars. This raised the possibility of a mild diabetes insipidus component, although that possibility was not formally tested. Bakheit and Behan also noted upregulation of hypothalamic serotonin receptors in postviral fatigue syndrome.[11]

Patients with severe chronic fatigue states are sometimes found to exhibit immune dysfunction with associated recurrent and persistent infections. Infections like persistent bowel cryptosporidium or fungal overgrowth also suggest an immune suppressed state. We suspect that the immunologic abnormalities may be secondary to adrenal dysfunction. Chronic severe fatigue, myalgias, arthralgias and neuropsychiatric changes are often associated with persistently elevated interferon levels.[14,15] Cortisol also lowers interferon levels.[16] Interestingly, metoclopramide and naloxone have been reported to improve interferon induced fatigue,[14,15] although we've not tried these medications. It would be interesting to test interferon levels before and after treatment with cortisol and see if levels correlate with symptomatic improvement, as elevated interferon can mimic or cause many of the symptoms and signs (for example, achiness, muscle mitochondrial changes, and fatigue) seen in chronic fatigue patients.[14,15]. This could offer another mechanism for cortisol's effectiveness. Other adrenal androgens (for example, testosterone, dehydroepiandrosterone [DHEA] and DHEA-S]) also have significant effects on lymphokine production[16] and lower levels in females could explain their increased susceptibility. We recently tested DHEA-S levels in three patients with abnormal cortrosyn tests and found DHEA-S levels to be very low. ACTH is widely accepted as a regulating factor for adrenal androgen secretion under certain conditions.[16] Further studies of interleukin (IL) 2, 4, and 5 function in these patients would help define the immune dysfunction further. DHEA, for example, increases IL-2 and gamma-interferon (gamma-IFN). Testosterone decreases IL-4, IL-5 and gamma-IFN. Glucocorticoids inhibit gamma-IFN and IL-2.[16] Although the cause of the immune dysfunction is not clear, the above suggest possible mechanisms by which hypothalamic suppression could be involved.

Jefferies[4,5] noted several decades ago that severe fatigue and recurrent URIs following a severe viral infection were often caused by adrenal insufficiency and resolved with cortisol treatment. He theorized that the fatigue was caused by a transient, and at times permanent, inhibition of ACTH production by the viral infection. This theory was recently supported by the work of Demitrack and Dale.[10] In several thousand patient years of experience, Jefferies found these patients improved dramatically on low-dose cortisol. There was no toxicity (except mild gastritis) as long as the dosage was physiologic [for example, 5 milligrams of cortisol tid to qid] and not pharmacologic.[4,5] Our findings support Jefferies' experience. Patients with low adrenal reserve (for example, no doubling in one hour) usually did well with 5 milligrams of cortisol qam and, if needed, 2.5 milligrams at lunch. Patients with low baselines were more likely to need 5 to 7.5 milligrams of cortisol tid to qid (up to 30 milligrams a day, with morning doses being higher). Dr. Jefferies recommends that any patient who does not respond to bid dosing be given a trial of 2.5 to 5 milligrams of cortisol po qid. Patients with reactive hypoglycemia were likely to be hypoadrenal, as cortisol helps to maintain blood glucose levels.

Although at times they are secondary to the immune or other dysfunctions, the fibromyalgia and the parasitic, bacterial, and fungal infections need to be treated as well or the patient's fatigue will persist. Fibromyalgia appears to be a common endpoint of many physical, physiologic, and/or psychological stress states. We view it as predominately a sleep disorder. These patients have multiple tender points and occasionally muscle trigger points which could interfere with deep sleep. These patients tend to toss and turn a lot at night and remain in light sleep stages. The quality of the deep sleep stages that "recharge their batteries" appears to be disordered. Thus, despite many hours of sleep, these patients can be considered to have not (effectively) slept for many years. The stress of sleeping ineffectively leaves the patient functioning poorly and may alter the HPA axis.[13] This stress can aggravate the tender points and thus, the cycle continues. Treatment needs to be geared toward restoring the duration, and/or quality, of deep-stage sleep and resolving the patient's trigger and tender points.

Dr. Janet Travell, the personal physician to Presidents Kennedy and Johnson, is also one of the world's foremost experts on myofascial pain. In the *Trigger Point Manual,* Dr. Travell's and Dr. David Simon's book on myofascial pain,[17] there is an excellent chapter on perpetuating factors that must be treated. Our experience suggests that the perpetuating factors in myofascial pain syndrome and fibromyalgia are similar. We have found the a mix of therapies will usually cause fibromyalgia to improve or fully resolve. Our regimen consists of (a) Treatment with 10 to 50 milligrams of amitriptyline hs or 25 to 150 milligrams of trazodone hs or 5 to 10 milligrams of cyclobenzaprine hs. (b) Nutritional support, for example, Berocca Plus (or TwinLab Daily One Cap) vitamins one a day long term plus two tablets of magnesium chloride (Slow Mag) tid for six months. Correcting low Vitamin B_{12} and iron levels is important. (c) It is important to treat even borderline hypothyroidism and hypoadrenalisin (as discussed previously). (d) Exercise (when the patient starts to improve). (e) For our refractory patients, we've found a form of neuromuscular reeducation [Trager—per Milton Trager, M.D.] to be very beneficial. (f) Correcting structural perpetuating factors such as uneven leg lengths, small hemipelvis, short upper arms (adjust chair arms), et cetera, is important. (g) As noted below, it is also important to treat any occult underlying infections.

Chronic fatigue patients often have a mix of underlying infections caused by (and perhaps aggravating) their immune dysfunction. We found that treating these was critical. Most patients had a marked decrease in their recurrent viral infections on cortisol. Chronic sinusitis, UTI, and other bacterial infections are readily detectable. Bowel yeast overgrowth is harder to test for and, therefore, we considered treating the patient empirically if they had frequent antibiotic use or frequent vaginal or dermatologic fungal infections (that is, suggestive of increased risk of or a decreased resistance to fungal infections]. We used 1 million units of nystatin po qid in this study. Our current experience suggests that adding 200 milligrams of itraconazole (Sporanox) po qd with food for three to four weeks, followed by 100 milligrams po qd (to the nystatin) may be more effective. Bowel parasites also needed to be treated and were surprisingly common (seven of nineteen patients tested). Samples should be obtained after a Phospho-Soda

laxative[6] and tested for in a lab familiar with parasite detection (see methods). Otherwise, the low sensitivity will make this an unreliable test.

In many patients, the above problems appear to be associated with increased nutritional needs. Many patients with only mild to moderate fatigue (and therefore not included in this series) have their symptoms resolve fully, simply by taking a TwinLab Daily One Cap vitamin or Berocca Plus qd and two 67-milligram tablets of magnesium chloride (Slow-Mag) tid, and avoiding excess sugar, caffeine, and alcohol. This is an important part of the regimen for the severely fatigued patient in our current series as well.

Lindenbaum et al.[18] found that barely subnormal or occasionally even normal B_{12} levels can be associated with evidence of severe neuropsychiatric changes caused by cobalamin deficiency—even in the absence of anemia or macrocytosis. These included memory loss, fatigue, and personality changes. Similar findings were noted by Carmel.[19] Norman[20] also noted that as many as 40 percent of B_{12}-deficient individuals may have been missed by simply relying on serum B_{12} levels. These were found by checking urine methylmalonic acid. Lindenbaum et al.'s recent study confirms that B_{12} deficiency can occur even with vitamin B_{12} levels over 500 pg/ml.[21] Because the level at which neuropsychiatric changes cease to occur is not well defined, a trial of B_{12} 1 milligram IM a week for eight weeks was given in some patients with levels of up to 540 pg/ml to rule out subclinical B_{12} deficiency. Surprisingly, twenty-four of twenty-six patients had significant improvement. Some patients benefit from continuing with B_{12} injections 1 milligram IM every three to five weeks. Most others did not need this after the initial series of injections. A trial of iron treatment was also considered if ferritin levels were less than 40 ng/ml.

As in any other illness, psychological factors, including depression, anxiety, and psychological conflicts, are critical here and must be addressed. We found that lack of interests correlated well with depression being primary [found in only four of sixty-four patients]. If the patient had many interests, but was frustrated over not having the energy to fulfill them, the depression was usually considered to be secondary to the fatigue. This is corroborated by the common finding of high baseline cortisols in patients whose

depression is primary. The frequency of low morning cortisol levels makes it unlikely that endogenous depression is common in chronic fatigue state patients.[12]

Patients may at times have intermittent exacerbations of their symptoms while physical and psychological issues are being worked through. Recurrence of previous problems (for example, low B_{12} or infections) occasionally occurs and requires retreatment. Continuing to guide and assist patients through this period is very important. Doing this, we have found that most patients maintained their improvement during the one to two year poststudy period.

Initially, we considered limiting the study to patients who met strict CFS (chronic fatigue syndrome) criteria. Recent reports, however, suggest that immunologic abnormalities seen in CFS patients [versus controls] are no different than those seen in other patients with severe fatigue.[22] Our experience also suggested that the underlying causes and the response to treatment were not affected by whether patients strictly met criteria for CFS. Because of these two reasons, we elected to study all patients who found their fatigue to be severe and persistent and whose constellation of symptoms was similar to CFS, even if they did not fulfill all of the criteria for CFS.

Ideally, we would have liked to have done a controlled crossover study for all variables and to test the effect of each treatment separately. Simultaneous treatment of the patient's underlying problems may be required, however, to cause the symptoms to resolve. We therefore chose, instead, to begin with an open clinical trial. At this point, we are planning a future controlled trial. Areas that would be good candidates for a controlled study within the above context would include: (1) Low-dose cortisol for patients with borderline low cortrosyn test baselines (cortisol of 6 to 13 mcg/dL) or borderline low adrenal reserve values; (2) A trial of itraconazole or fluconazole versus placebo in patients with recurrent fungal infections; (3) B_{12} injections as above versus placebo for patients with B_{12} levels of 208 to 540 pg/ml. The controlled trial may also decrease the problem of defining clearly which treatments are causing the improvement, as several treatments were often begun simultaneously.

Much of our experience confirms the old adage that "even a blind squirrel finds acorns." We are certain that there is much more to learn in this area. In the interim, it is

hoped that the above report creates new avenues to explore in understanding the treatment of severe chronic fatigue.

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Copies of both of these studies are available from the Haworth Document Delivery Service (800–342–9678) or can be downloaded from www.endfatigue.com.