EXERCISE LIMITS IN CHRONIC FATIGUE SYNDROME

To the Editor:

Sisto et al[1] concluded in their recent paper, "Metabolic and cardiovascular effects of a progressive exercise test in patients with chronic fatigue syndrome (CFS)"[1] that "our CFS group could withstand a maximal treadmill exercise test without a major exacerbation in either fatigue or other symptoms of their illness." Having managed hundreds of patients with CFS (PWCs) over the past 10 years, it has been my experience that the stress of an office visit—nevertheless maximal exercise testing—typically relapses them. To demonstrate this, Dr. David Bell, Cindy Voyles, PA, and I asked 31 consecutive new patients with CFS to record their symptoms on a simple integer scale starting 3 weeks before until 12 days after maximal exercise testing. We used an electronically braked bicycle ergometer on which the work of peddling increased steadily with time instead of slowly increasing treadmill stages alternating with rest periods, as was described by Sisto. Our work rate (ramp) was chosen so that the subject would be expected to reach his/her maximum oxygen consumption (VO_2 max) within 8 to 10 minutes of exercise (about 40 minutes in the Sisto paper). The **Figure** summarizes our findings by averaging all the results for the symptom "fatigue." In particular, 23 (74%) experienced worsening fatigue and 8 (26%) stayed about the same after maximal exercise. None improved. The average relapse lasted 8.82 days, although 12 subjects (22%) were still in relapse when the study ended at 12 days. Interestingly, we found similar changes with exercise in lymph pain, depression, abdominal pain, sleep quality, joint and muscle pain, headache, and sore throat.

Taken together, Sisto's results and our results are extremely important in understanding "relapse" in PWCs, especially with respect to the work that PWCs can perform safely. The data would suggest that when PWCs are pushed to maximal exertion, they frequently relapse for long periods of time. On the other hand, PWCs were able to withstand long periods of activity on Sisto's protocol, where maximal exercise was preceded by a slow warm-up period characterized by light activity alternating with rest. Assuming that Sisto's subjects were moderately ill and that their instrument for measuring fatigue reflected accurately (as we are assured in the article), one might conclude that PWCs can perform mild to moderate exercise (or work) without relapse, providing they have frequent rest periods. This concept forms the basis of our current activity recommendations to limit exercise to less than 5 minutes followed by rest. This work-rest cycle may be repeated several times daily in order to maintain strength, flexibility, and conditioning.

These two studies provide a sound basis for the exercise prescription in CFS, but they have widespread insurance and disability implications as well. I strongly encourage other exercise physiologists to study this phenomenon further.

Charles W. Lapp, MD
Duke University Medical Center,
Durham, North Carolina
Hunter-Hopkins Center, PA,
Charlotte, North Carolina

1. Sisto SA, LaManca J, Cordero DL, et al. Metabolic and cardiovascular effects of a progressive

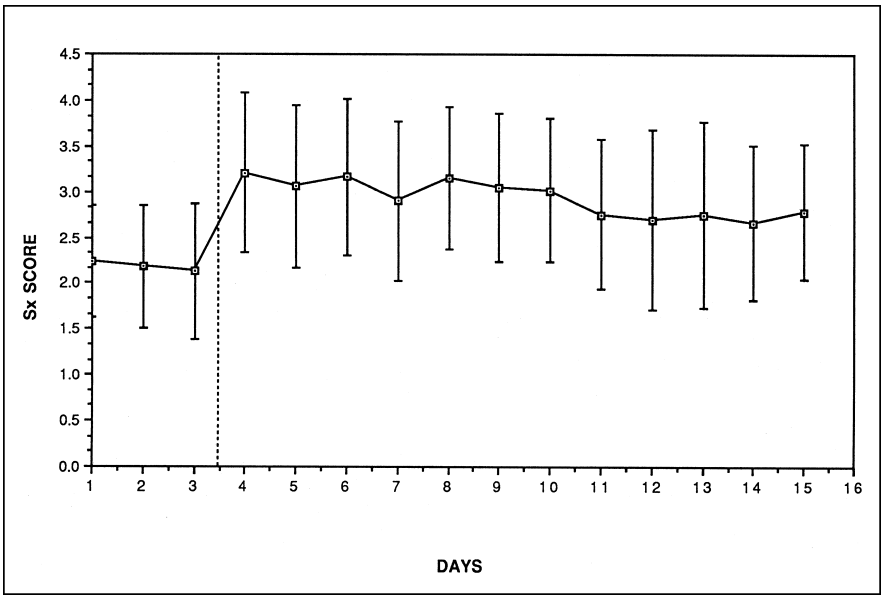

Figure. Change in fatigue after exercise.

exercise test in patients with chronic fatigue syndrome. *Am J Med.* 1996;100:634–640.

Manuscript submitted September 9, 1996 and accepted December 17, 1996.

The Reply:

Dr. Lapp's major concern appears to be our conclusion that our CFS group could withstand a maximal exercise test without a major exacerbation in either fatigue or other symptoms of their illness. He indicates a worsening of the symptom of fatigue over 12 days after exercise in the majority of his cases studied using a simple integer scale of fatigue. Dr. Lapp interprets his data to indicate that patients frequently "relapse" after strenuous exercise. There are several possibilities for the apparent discrepancy in outcome between Dr. Lapp's work and our own.

First, our exercise protocol required subjects to walk at moderate rates interspersed with rest periods. But after these rests, the protocol followed a standard regimen of progressive ramping without rests until the patient could no longer continue. Only one patient reported that she had to spend substantially more time in bed with markedly worsened symptoms. Having learned that this protocol does not cause major illness exacerbation, we have since completed a follow-up treadmill study in which subjects attain a VO_2max in 8 to 10 minutes. Using this protocol, again most patients did not report a serious exacerbation of their illness. So the use of rest periods in our initial protocol does not explain any differences between Dr. Lapp's observations and our own.

Second, we may be seeing the same outcomes after strenuous exercise but simply labeling them differently. Since CFS patients rarely show the sort of symptom exacerbation that would be needed to allow one to see a "relapse," we prefer to call a worsening of symptoms a "flare-up." Dr. Lapp's data, as well as our own, report increases in fatigue self-ratings after strenuous exercise. However, does an increase in self-rated fatigue from averages of 2.3 to 3 on a 5-point Likert scale, as seen in Dr. Lapp's data, constitute a relapse? Simply knowing that self-reported fatigue is significantly worse after exertion does not answer that question. How to do this is an important goal in CFS research. Our center is evaluating the complaint of postexertional exacerbation of CFS symptoms with activity monitoring and use of ambulatory diaries.

Third, the constitution of the patients that Dr. Lapp studied may have been different than ours. Dr. Lapp's medical practice probably sees a wide range of CFS patients. Based on the literature, we can expect that many of his patients have concurrent or life-long psychiatric diagnoses.[2,3] In contrast, the patients in our study were highly selected, and none had a psychiatric diagnosis in the 5 years prior to their illness onset. This is an important issue because it is known that people with psychiatric disorders have an increased frequency of somatic complaints relative to people without psychiatric disorders.[1,4] Thus, Dr. Lapp's patients may have been more sensitive to postexertional symptoms than our patients.

Finally, we do not believe the protocol that we used in our study can be used as a rationale for developing an exercise prescription for CFS. We did not design the progression of our treadmill protocol to draw conclusions about the prescription of exercise but rather to achieve a maximal effort without the risk of exacerbation of symptoms. Therefore, to reason that our discontinuous treadmill protocol could be likened to a graduated exercise program may lead to problematic conclusions. However, the fact that a patient can tolerate such a test certainly can be used as evidence to help convince CFS patients who are similar to those in our study that increasing exercise is possible without a significant risk.

Sue Ann Sisto, MA, PT
John LaManca, PhD
Benjamin Natelson, MD
CFS Cooperative
Research Center
UMDNJ-New Jersey
Medical School
Newark, New Jersey

1. Katon W, Russo J. CFS criteria: a critique of the requirement for multiple physical complaints. *Arch Intern Med.* 1992;152:1604–1609.
2. Kruesi MJP, Dale J, Straus SE. Psychiatric diagnoses in patients who have chronic fatigue. *J Clin Psychiat.* 1989;20:53–56.
3. Lane TJ, Manu T, Matthews D. Depression and somatization in the chronic fatigue syndrome. *Am J Med.* 1991;91:335–334.
4. Simon GE, Vonkorff M. Somatization and psychiatric disorder in the NIMH epidemiologic catchment area study. *Am J Psychiat.* 1991;148:1494–1500.

Manuscript submitted December 3, 1996, and accepted December 17, 1996.

GRADED EXERCISE TESTING AND CHRONIC FATIGUE SYNDROME

To the Editor:

We were interested in the study of Sisto et al[1] who described results of graded exercise testing among 21 individuals with the chronic fatigue syndrome (CFS) and matched sedentary controls. The authors concluded that CFS patients have low fitness and that reduced aerobic endurance is not due to metabolic or cardiovascular limitations to exercise. We want to add to their findings and propose that the observed low oxygen uptake may be due to still other factors than deconditioning.

Similar to the authors, we performed pretreatment graded treadmill tests to exhaustion for 26 patients (19 women and 7 men) meeting the criteria for CFS,[2] who were participants in a drug treatment study. Heart rate and blood pressure were measured every 2 minutes, and oxygen uptake (VO_2)

TABLE

Variables at Peak Stage of Maximal Treadmill Test

	Number of Subjects	Age (Years)	Height (cm)	Weight (kg)	Heart Rate (bpm)	Peak Oxygen Uptake (mL kg min)	RER°
OHSU-MAX	14	40 ± 10	170 ± 5	68.8 ± 11.4	153 ± 21	23.4 ± 7.6	1.17 ± 0.13
OHSU-NOMAX	5	38 ± 10	164 ± 10	69.5 ± 14.2	134 ± 13	15.3 ± 4.8	0.92 ± 0.09
SISTO-MAX	10	35 ± 11	167 ± 6	70.0 ± 10.7	176 ± 12	28.1 ± 5.1	1.10 ± 0.10
SISTO-NOMAX	11	34 ± 9	162 ± 2	69.0 ± 14.5	146 ± 21	23.9 ± 5.6	1.00 ± 0.10

Data are mean ± SD.
OHSU = our subjects; SISTO = individuals reported by Sisto et al; MAX = individuals meeting criteria for achieving maximum oxygen uptake; NOMAX = individuals not meeting criteria for achieving maximum oxygen uptake; RER = respiratory exchange ratio (VCO_2/VO_2).

and minute ventilation were measured at 20-second intervals during and immediately after exercise. Our results and Sisto's findings are shown in the **Table.** We compared only our women subjects to eliminate potential gender differences.

Sisto et al found CFS patients and sedentary controls had comparable mean values for both peak VO_2 and VO_2 at the ventilatory threshold. Because of those results, they concluded that all CFS patients' decreased aerobic capacity was due to lack of exercise conditioning.[1] Although we found slightly lower end-exercise heart rate and VO_2, we agree that CSF subjects' average peak VO_2 values are not different than matched nonexercising individuals.

However, we disagree with the conclusion that a muscle metabolic abnormality has been excluded. Among patients with CFS, the range of values is wide. For example, among our subjects achieving a respiratory exchange ratio greater than 1.0, peak VO_2 varied from 15.0 to 41.0 mL kg per hour. Besides measurement of peak VO_2, the pattern of an individual's progressive minute ventilation and VO_2 values can provide clues to patients with mitochondrial defects, glycogen storage diseases and lipid myopathies, some of whom may respond to specific therapy.[3]

The pathogenesis of CFS is not known. Abnormalities of muscle histology and metabolism have been reported among CFS patients,[4,5] and a subset of these individuals may have metabolic myopathies as a manifestation of their illness. Until the syndrome's pathophysiology is discerned, a marked reduction of peak VO_2 should not be interpreted as part of a "normal" response range. Graded exercise testing, with continuous measurement of ventilatory parameters and VO_2, may provide additional documentation of disability, evidence of a muscle disorder, and assist understanding and managing these patients' illness.

Diane L. Elliot, MD
Linn Goldberg, MD
Mark O. Loveless, MD
Department of Medicine
Oregon Health Sciences University
Portland, Oregon

1. Sisto SA, LaManca J, Cordero DL, et al. Metabolic and cardiovascular effects of a progressive exercise test in patients with chronic fatigue syndrome. *Am J Med*. 1996;100:634–640.
2. Feduka 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.
3. Elliot DL, Buist NRM, Goldberg L, et al. Metabolic myopathies: evaluation by graded exercise testing. *Medicine*. 1989;68:163–172.
4. Wassif WS, Sherman D, Salisbury JR, Peters TJ. Use of dynamic tests of muscle function and histomorphometry of quadriceps muscle biopsies in the investigation of patients with chronic alcohol misuse and chronic fatigue syndrome. *Ann Clin Biochem*. 1994;31:462–468.
5. Barnes PR, Taylor DJ, Kemp GJ, Radda GK. Skeletal muscle bioenergetics in the chronic fatigue syndrome. *J Neurol Neurosurg Psychiat*. 1993;56:679–683.

Manuscript submitted October 28, 1996 and accepted December 13, 1996.

The Reply:

The major concern of Drs. Elliot, Goldberg, and Loveless appears to be our conclusion that significant muscle metabolic abnormality can be excluded based on our gas exchange threshold (GET) results. Our conclusion that the lack of group differences in the GET is strong evidence that the CFS patients do not have a significant metabolic defect in their muscle glycolytic pathway refers to the mean GET for the CFS group in this study. However, there may have been CFS patients in the group that we studied who had subtle muscle metabolic problems. This possibility is substantiated by our recent study[1] of muscle bioenergetics in CFS patients that indicated a reduced oxidative muscle metabolism in some CFS subjects as indicated by delayed phosphocreatine uptake time during magnetic resonance spectroscopy compared with sedentary healthy controls. The explanation for the results of the McCully et al[1] study is the possibility of subtle mitochondria abnormalities.

Drs. Elliot, Goldberg, and Loveless also comment that a marked reduction in peak VO_2 should not be interpreted as part of a "normal" response range. They provide peak oxygen uptake values for their CFS patients who obtained a maximal effort and those who did not, compared with ours. However, using the American College of Sports Medicine guide-

lines, our mean peak VO_2 values for the CFS group fell within the low end of the "normal" maximal oxygen capacity range, indicating no significant cardiopulmonary deficits. Here again, a small subset of the CFS women who we studied may have had a much lower peak VO_2 than the group average (Sisto et al, peak VO_2 range CFS 13.3 to 37.0 mL/kg/min versus Elliot et al, peak VO_2 range 15.0 to 41.0 mL/kg/min). One possibility may be that the Oregon CFS sample was slightly less fit than ours. Another possibility for differences in peak VO_2 between our groups may be that we chose stricter criteria for identifying those patients who attained a metabolic maximum; consistent with that is the fact that relatively fewer of their patients stopped exercising prior to attaining criteria compared with our group. Further research is needed to determine whether CFS patients who have low VO_2 in combination with very low ventilatory thresholds have true muscle mitochondrial deficits.

Sue Ann Sisto, PhD, PT
John LaManca, PhD
Benjamin Natelson, MD
CFS Cooperative
Research Center
UMDNJ-New Jersey
Medical School
Newark, New Jersey

1. McCully KK, Natelson B, Iotti S, et al. Reduced oxidative muscle metabolism in chronic fatigue syndrome. *Muscle Nerve.* 1996;19:621–625.

Manuscript submitted December 6, 1996 and accepted December 13, 1996.

ERRATA

Weber BE, Kapoor WN. Evaluation and outcomes of patients with palpitations. *Am J Med.* 1996;100: 138–148. In a re-review of their data, the authors have found the following clinically minor discrepancy:

In Table III, line 11 states:

Aortic insufficiency	2	1.1%

It should state:

Aortic insufficiency	1	0.5%
Sinus tachycardia	1	0.5%

Willard KE, Johnson JR, Connelly DP. Radical improvements in the display of clinical microbiology results: a web-based clinical information system. *Am J Med.* 1996;101:541–549.

The listed sequence of authors in this article should have been: Willard KE, Connelly DP, Johnson JR.