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ASTHENIA AND THE CHRONIC FATIGUE SYNDROME

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Patients with chronic fatigue syndrome (CFS) complain of severe, persistent fatigue that cannot be accounted for by any known medical disease. Because fatigue occurs in certain neuromuscular diseases, neurologists and neuromuscular specialists are often asked to evaluate these patients, but the results are nearly always negative. Indeed, a careful analysis of the symptoms of CFS patients suggests that the fatigue that they describe differs radically from the kind of fatigue experienced by patients with neuromuscular disease. A closer look at the different meanings of the term ''fatigue'' should help to clarify the nature of CFS, facilitate the clinical evaluation of patients, and perhaps prevent unnecessary laboratory investigations.

At least four varieties of fatigue can be distinguished.[9] The physiological or laboratory definition of fatigue is simply an inability to sustain a specified force or work rate during exercise. This can be termed *objective fatigue*. In a clinical setting, exercise can also be limited by unpleasant sensations such as muscle pain, dyspnea, and tachycardia. This is *subjective fatigue,* in the sense that discomfort inhibits the wish to continue exercising; but that discomfort arises from objective physiological causes. After prolonged exercise, athletes may collapse from general exhaustion caused by hyperthermia, dehydration, hypovolemia, hypotension, and hypoglycemia. This is nonmuscular or *systemic fatigue*. Finally, many patients complain of general weakness, tiredness, and exhaustion after minor exertion, and a reluctance to undertake physical or mental activity. Such patients are not truly weak, and they do not exhibit abnormal physiological responses to exercise. This symptom is evidently of cerebral rather than neuromuscular origin. I prefer to use the term *asthenia* for this type of fatigue, which is characteristic of CFS as well as of a number of other medical and neurological disorders.

For each type of fatigue there are normal and abnormal examples. Objective fatigue is evident in normal persons as a rapid decline of muscle force during sustained, maximal, isometric contraction, such as occurs during weight lifting. This is a failure of contractile function, since muscle electrical activity is preserved; it appears to be correlated with rising intracellular levels of dihydrogen phosphate ions.[16] In another setting, endurance during prolonged, vigorous exercise (such as cross-country skiing) is dependent on the amount of glycogen remaining in the muscles. When glycogen is used up, the muscles are forced to get nearly all of their energy from the oxidation of lipids, a process that cannot sustain a work rate greater than 50% of maximal capacity.[12] In McArdle disease, muscle force and electrical activity decline abnormally during repetitive nerve stimulation, because of a progressive failure of muscle membrane excitability.[5] A similar phenomenon occurs subclinically in several myotonic disorders,[1] and transient weakness during exercise is apparent clinically in autosomal-recessive myotonia congenita. Of course, the most familiar example of pathological fatigue is myasthenia gravis, a disease in which weakness increases during exercise because of progressive blockade of neuromuscular transmission. Patients with multiple sclerosis sometimes develop transient leg weakness during exercise, probably because of blocked axonal transmission within demyelinated corticospinal tracts.

In normal persons, lactic acidosis begins to appear when the rate of exercise exceeds the ''anaerobic threshold,'' approximately one half of the maximal exercise capacity. Acidosis causes tachycardia and hyperpnea, and as acidosis increases these unpleasant sensations tend to limit exercise.[15] This is subjective fatigue, since exercise is limited by distress rather than by weakness. Athletic training shifts the

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anaerobic threshold to higher work rates, by increasing both the oxidative capacity of muscle and the maximal exercise capacity. Prolonged inactivity (''deconditioning'') has the reverse effect. Muscle discomfort during exercise is not usually a limiting factor in normal persons. However, patients with occlusive peripheral vascular disease experience unbearable pain in exercising muscles (intermittent claudication). This pain presumably results from the release of unidentified pain-inducing substances from ischemic muscle, and is not accompanied by muscle spasm or cramp. Patients with severe anemia, low cardiac output, or pulmonary disease have a reduced exercise capacity because of excessive tachypnea and hyperpnea during exercise. Various metabolic myopathies also impair exercise tolerance by causing subjective fatigue. McArdle disease causes exertional muscle pain and cramps, while mitochrondrial myopathies cause the cardiopulmonary symptoms of excessive lactic acidosis. The latter condition is sometimes hard to distinguish from a deconditioned state in normal persons.

General exhaustion or systemic fatigue is the reason that some runners collapse at the end of a marathon race. Heat exhaustion is a similar phenomenon. Patients with systemic carnitine deficiency, autonomic insufficiency, or hypoglycemia may suffer a similar decompensation during ordinary exercise.

In contrast to the above fatigue syndromes, the inability of patients with asthenia to carry out ordinary daily activities cannot be explained by any abnormality in the neuromuscular apparatus or by hypoglycemia, hypotension, vascular disease, or cardiopulmonary insufficiency. In some cases, feelings of lassitude and exhaustion come and go, periods of normal activity alternating with periods of exhaustion; in others, the sensation of fatigue is constant. Some patients feel tired before exercise starts; others function fairly well in the morning and then ''crash,'' overwhelmed by an exhausted feeling that may last for hours or days. Asthenia is best described as lack of ''energy,'' ''pep,'' or motivation; it takes more than normal effort to undertake both physical and mental activities. These characteristics suggest that asthenia is a state of mind, pertaining to will and motivation.

Everyone is familiar with asthenia as the symptom referred to in the term ''prostrating illness.'' The need to curl up and hide, perhaps in order to escape predators and to reduce energy expenditure, may well be a behavior selected by evolution to increase an animal's chances of surviving wounds and infections.[7] Like fever and anorexia, two other protective reactions to illness, asthenia may result from the action of cytokines on the brain, but neither the cytokine nor the site of action has been identified. At any rate, asthenia is a normal response to systemic illness. It occurs both in acute infections and in chronic, debilitating illnesses like uremia, liver disease, hypothyroidism, hypoadrenalism, tuberculosis, HIV infection, cancer, and collagen–vascular diseases. Transient asthenia is common following major surgery, typically lasting several weeks. Interestingly, asthenia occurs frequently in multiple sclerosis, a disease with no overt involvement outside the central nervous system. Multiple sclerosis patients with fatigue have been reported to show decreased glucose metabolism in frontal cortex and basal ganglia.[14] Asthenia is also a common side effect of beta-blocking drugs. Exercise tests show that subjects taking propranolol have a normal exercise capacity but feel that they must make a greater effort to achieve a given work rate.[8]

To return to patients with CFS, there is both negative and positive evidence that their fatigue complaints belong in the category of asthenia. There is no weakness on clinical examination, and electromyography, serum enzymes, and muscle biopsy are invariably normal.[6] Reliable studies of exercise physiology, including nuclear magnetic resonance spectroscopy, have shown no abnormality, other than deconditioning in some cases.[6,11] Some patients have an exaggerated cardiopulmonary response to exercise; this can be accounted for by either deconditioning or automonic instability. Da Costa reported these phenomena as ''irritable heart'' in soldiers during the American Civil War,[4] and the same syndrome received medical attention during the two World Wars.[17] CFS patients who feel exhausted do not exhibit hypoglycemia, hypotension, or any of the other objective features of systemic fatigue. Furthermore, the fatigue symptoms of CFS have the characteristic positive features of asthenia, as described above. Many such patients are unable to perform ordinary daily activities, yet they perform normally in the doctor's office.

Is there any evidence that CFS is caused by a systemic illness? The majority of patients have multiple somatic symptoms referrable to several different organ systems, yet no abnormalities are found on physical examination or laboratory tests. In this respect, CFS differs from every known medical disease. Even so, many medical explanations for CFS have been proposed, but despite the ardent claims of CFS patients and their physician allies, none has been substantiated. The history of these fad diagnoses dates back at least to the nineteenth century, and includes entities such as soldier's heart, mitral valve

prolapse, functional hypoglycemia, iron deficiency, vitamin deficiency, food allergy, and multiple chemical sensitivities. Infectious etiologies have been especially popular, from chronic brucellosis to systemic candidiasis to chronic Epstein–Barr virus infection, but no infectious cause has been proven.[3] Currently some sort of immune disorder is often invoked, but the immune abnormalities that have been reported are minor, inconsistent, and contradictory.[10]

In the latter nineteenth century, the American neurologist George Beard coined the terms ''neurasthenia'' and ''nervous exhaustion'' for a syndrome indistinguishable from CFS.[2] He believed that nervous energy was literally depleted, like a rundown battery, and needed to be restored by rest and other measures. This psychiatric diagnosis was popular for about 40 years, eventually being replaced by entities such as depression, anxiety neurosis, and somatization. Asthenia is one of the cardinal symptoms of major depression, along with insomnia, anorexia, weight loss, and constipation. Typically all of these vegetative symptoms resolve following recovery from depression. These similarities have encouraged some physicians to assert that CFS is simply depression in disguise, but that view oversimplifies the problem. It is true that insomnia, mood changes, and other psychological symptoms are present in the majority of CFS patients. Between half and three fourths of CFS patients have a lifetime history of major depression, a much higher proportion than in patients with other medical conditions such as rheumatoid arthritis. However, only a minority of CFS patients have currently diagnosable major depression, and most patients do not benefit much from antidepressant drug therapy.[8] Clearly, there is an important link between depressive disorder and CFS, but the connection is indirect. Until we know more about the neurophysiology of asthenia, the nature of this connection must remain speculative.

When evaluating a patient with the typical clinical features of asthenia, there is usually no need for an extensive workup. It is useful to perform a simple office test of exercise capacity, such as climbing stairs or walking briskly for 5–10 min, recording pulse and respiratory rate and testing muscle strength before and after exercise. This procedure will often document better exercise tolerance than the patient had described. The main aim of laboratory investigations is to exclude some kind of occult systemic disease. Assuming that there is no clue from physical examination, a reasonable set of screening tests would consist of complete blood count, sedimentation rate, serum creatine kinase, antinuclear antibody, thyroid and adrenal function tests, electrolyte panel, chemistry panel, and chest radiography. There is usually no need for electrodiagnostic tests or muscle biopsy, and exercise physiology tests should be reserved for cases in which there is a strong suspicion of a mitochondrial myopathy.

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