

Chronic Fatigue: Symptom and Syndrome

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Chronic fatigue is common, is difficult to measure, can be associated with considerable morbidity, and is rarely a subject of controversy. The chronic fatigue syndrome also presents problems in definition and measurement, is associated with even more morbidity than chronic fatigue itself, and is often controversial. Particularly unclear is the way in which chronic fatigue and the chronic fatigue syndrome relate to each other: Is one the severe form of the other, or are they qualitatively and quantitatively different? We know that many things can cause chronic fatigue, and this is probably true for the chronic fatigue syndrome, too. We can anticipate that discrete causes of the chronic fatigue syndrome will be found in the future, even if these causes are

unlikely to fall neatly along the physical–psychological divide that some expect. The causes of chronic fatigue are undoubtedly many, both in a population and in any individual person, even when a discrete cause, such as depression or cancer, is identified. Social, behavioral, and psychological variables are important in both chronic fatigue and the chronic fatigue syndrome. Interventions that address these general variables can be successful, and currently they are often more successful than interventions directed at specific causes.

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The symptom of fatigue remains elusive and fascinating. Of all the symptoms discussed at the Regenstein Conference, none has the potential to arouse as much bafflement and controversy as this one. First, the symptom is ubiquitous. The association between fatigue and nearly every condition covered in *The Oxford Textbook of Medicine* or *The Oxford Textbook of Psychiatry* means that the symptom tends to be held in low esteem by physicians and that the presence of fatigue gives little specific diagnostic information (1). Second, the lack of congruence between the patient's report of feeling tired and exhausted and objective measures of fatigability (whether neuropsychological or physiologic) further frustrates clinicians and investigators. Finally, the chronic fatigue syndrome, a condition that has excessive fatigue and fatigability at its heart, has come to symbolize much of the frustrations and limitations of modern medicine (2).

After years of relative neglect, the subject of fatigue has, for many reasons, returned to center stage. A database maintained in the Department of Psychological Medicine at Guy's, King's, and St Thomas' School of Medicine now contains more than 3000 references, 300 of which were added in 1999 alone. It is impossible to do justice here to such a complex subject, so instead I consider only the nature of fatigue, its measurement, and the relationship between fatigue and the chronic fatigue syndrome. I conclude with some observations on treatment and the way forward.

MEASURING AND DEFINING FATIGUE

It is almost unnecessary to again draw attention to the ubiquity of the symptom of fatigue. Numerous population studies all confirm that fatigue is always among the most common somatic symptoms; in many studies, it is the most common. The prevalence depends on measurement and definition, but whenever many symptoms are considered together, fatigue is in the top three.

Fatigue is not something that one has or does not have. We all experience fatigue, but some have it for longer periods or at a greater intensity than others. To quote the late Geoffrey Rose (3), "the real question in population studies is not 'Has he got it?', but 'How much of it has he got?'". In both the community and primary care settings, fatigue, like almost every somatic or psychological symptom, follows a normal distribution (4, 5).

Fatigue as it occurs in the community resists simple measurement. When patients or clinicians refer to fatigue, they use the term differently than physiologists do. Fatigue as defined by the physiologist—loss of power over time, first described by Mosso and his ergograph (6)—differs greatly from the subjective fatigue experienced by patients. Put simply, 20% or 30% of the population has chronic fatigue, but these people are not abnormally fatigable. Although the literature is not unanimous, compelling evidence of abnormal neuromuscular fatigability in patients with the chronic fatigue syndrome is also lacking. After World War I, one of the

tasks of the British Industrial Fatigue Board was to develop a measure of fatigue. This enterprise failed (7); the conclusion was that it was impossible to test for fatigue.

This difficulty of measuring fatigue stems from the multidimensional nature of the condition. For example, for neurophysiologists, fatigue can be a mechanism open to precise definition and measurement and exemplified by such conditions as myasthenia gravis. Fatigue can also be a mechanism studied by neuropsychologists—here one encounters studies of progressive failure of cognitive performance on formal testing or attempts to use information processing theory to explore the idea that fatigue can be explained by the limited capacity of the nervous system. Fatigue can also be related to psychological variables, such as belief and expectation, and experimental evidence now suggests that a person's beliefs about fatigue can influence performance.

However, fatigue is also a feeling state, and a fundamental part of our current understanding of fatigue is that the feeling of fatigue is distinct from, and barely overlaps with, the behavioral aspects of performance decrement. The number of synonyms that exist for fatigue—lack of energy, weakness, effort, sleepiness, tiredness, lassitude, and so on—indicates the magnitude of the nosologic task. Similarly, general fatigue seems to be twice as common as exhaustion (8) and nearly 10 times more common than feeling “generally run down” (9). Small changes in the wording used to ask patients about fatigue or postexertional malaise can profoundly affect prevalence (Jason L. Personal communication). Different groups also use terms in different ways; for example, of 16 adjectives used by psychiatrists to signify sadness, 6 were applied by patients to states of fatigue (10).

THE CHOICE OF MEASURES

Objective measures of fatigue, independent of the subjective experience of the patient, remain an unattainable Holy Grail. However, investigators have made progress in measuring the subjective symptom of fatigue, and numerous scales are available for this purpose. Some, such as the Fatigue Severity Scale (11) and the Profile of Fatigue Related Symptoms (12), measure several dimensions of illness, such as symptoms and disability. Others, such as the Chalder Scale (13), try to restrict themselves to mental and physical fatigue alone. There is no clear consensus on whether multidimensional or unidimensional measures are preferable (14); I try to use

one measure for one dimension and hence separately measure mood, fatigue, symptoms, and disability. The issues involved in this are comprehensively discussed by Jason and Friedberg (15).

IS FATIGUE HETEROGENEOUS, MULTIFACTORIAL, OR BOTH?

Clearly, fatigue has many causes. The differential diagnosis of fatigue in clinical practice is beyond the scope of this paper, but where discrete causes exist, the combination of history, physical and mental examination, and routine laboratory testing reveals the cause or at least identifies patients for whom further pursuit is worthwhile (16).

In addition to the fact that many discrete conditions cause fatigue (heterogeneity), the causes of fatigue may be multifactorial in the same person. For example, the literature on the occurrence and nature of fatigue in numerous discrete diagnostic categories, such as cancer (17), neurologic diseases (18), and rheumatologic diseases (19), is rapidly expanding. Almost invariably, fatigue is found to be common and to be associated with considerable distress and disability. However, most studies fail to link measures of individual disease activity with subjective fatigue; instead, depression, beliefs about illness, and lack of activity figure more prominently (20, 21). It is simple to postulate many discrete mechanisms for fatigue in disparate physical illnesses (22), but it is more difficult to pin these down in practice. Similarly, just as experts debate whether pain due to cancer should be considered, *sui generis*, as different from chronic nonmalignant pain (with the lumpers gaining ground over the splitters), similar arguments can be found in the literature on chronic fatigue.

It is when we move out of the literature on fatigue and discrete disease categories to the wider problem of fatigue in the community or primary care settings, where discrete causes are uncommon (23), that the evidence for multiple simultaneous causes of fatigue becomes overwhelming. I know of no population-based study that has not found chronic fatigue to be associated with a range of variables: demographic, social, cultural, physical, behavioral, and psychological (2, 24–28).

SO WHAT ABOUT THE CHRONIC FATIGUE SYNDROME?

Two conceptual ways to address the problem of the chronic fatigue syndrome are available. First, is the rela-

relationship between chronic fatigue and the chronic fatigue syndrome the same as that between moderate hypertension and severe hypertension? In other words, is the chronic fatigue syndrome associated with greater morbidity than but not fundamentally different from chronic fatigue? Or are the two conditions different beasts entirely? Should we lump or split? At the moment, we don't know, but it is worth analyzing the question itself because of some unexpected insights it gives us. It is a relief to note that in general, we have moved on from one form of splitting: the tedious and repetitive rhetoric that pits the "it's real" against the "oh no it's not" lobbies, which generate much heat and little light. However, what has succeeded this is a debate about subgroups. Is there one chronic fatigue syndrome, or many? Is there one somatic syndrome, or many?

The first argument concerns whether the chronic fatigue syndrome can be considered distinct from all of the other topics being discussed at Regenstrief Conference. The literature on the various symptom-defined conditions indicates that many have tried but failed to produce firm evidence of clear-cut, meaningful distinctions among, for example, the chronic fatigue syndrome, fibromyalgia, and the irritable bowel syndrome (29). It has therefore been argued that splitting these conditions up solely on the basis of symptoms alone (as all current definitions do) is not meaningful and that the current symptom-based definitions do not "cleave nature at the joints" (30). This is not to say that all patients with unexplained symptoms are the same; it is rather to say that the boundaries between certain conditions are not currently visible. With a greater knowledge of pathophysiology we will no doubt do better, but until we know where the divisions are, a healthy skepticism toward premature splitting is necessary.

The next argument is that chronic fatigue syndrome is a broad category and that it must contain several subgroups. Although this theory is plausible, considerable uncertainty exists about what the subgroups might be. Post hoc subgroup analysis is notoriously prone to error, but accumulating evidence suggests that dividing patients up according to whether the onset of fatigue is acute or insidious has merit (31, 32). Meanwhile, Hickie and colleagues (33) have found evidence suggesting that patients with long duration of illness and ill-defined onset (which make up the minority of cases) differ from pa-

tients with less disability and shorter duration of illness (which make up the majority). The former overlap with the psychiatric concept of somatization disorder and probably have a poor prognosis, whereas the investigators label the latter cases of "acquired neurasthenia" (33). The patients with less disability and shorter duration of illness may be the group in which we are most likely to find evidence of discrete etiologic triggers, such as infection, whereas the patients with insidious onset may prove to be the most difficult to treat.

Some of the desire to split the chronic fatigue syndrome into subgroups is driven by emotion. It isn't hard to argue that numerous causes are operative and that at some future date, identification of these causes will lead to a subdivision of the chronic fatigue syndrome. Given that the syndrome is still defined as much by what it is not as by what it is, this division is inevitable. It has been suggested that to assume that "the chronic fatigue syndrome" exists is like assuming the existence of a chronic abdominal pain disorder before it is classified into a disease of the gall bladder, colon, or appendix. However, such an argument may carry the subtext that the division will neatly separate physical and psychological causes, and it is implicitly (and sometimes explicitly) assumed that alongside the psychological chaff will be found the physical wheat. It is also interesting to note how some of those who advance this argument assume that "their" condition (the one they suffer from, research, or treat) will fall on the physical side of the divide. However, existing data run somewhat counter to these arguments: The greater the number of symptoms and the greater the perceived disability, the more likely clinicians are to identify psychological, behavioral, or social contributors to illness.

One last caution: When advances in our understanding of pathophysiology permit further divisions of what we currently label the chronic fatigue syndrome, we should remember the message of the literature on fatigue in well-established diagnostic categories. Fatigue can have more than one simultaneous cause, even when it is associated with a clear diagnosis. Mood, behavior, activity, and belief are important in understanding fatigue across a range of diagnostic categories, from cancer to cirrhosis; why should the chronic fatigue syndrome be any different, even when more causes are identified and the boundaries of the definition shift?

WHY DO WE NEED CRITERIA FOR THE CHRONIC FATIGUE SYNDROME?

The need for criteria for the chronic fatigue syndrome comes from two sources. The first is the research community. Without criteria, meaningful comparisons between studies become impossible, and the introduction of such criteria has been a prerequisite for the current research effort. But we must not forget that our operational criteria for something we call “the chronic fatigue syndrome” is just that—operational criteria to allow research to be done. The existence of the criteria does not mean that there is a disorder that corresponds to the criteria. The criteria operationalize, but they do not reify.

The pressure to reify the chronic fatigue syndrome also comes from the way in which the developed world organizes medical services and reimbursement systems. There have always been sound financial reasons for each medical specialty to develop its own unexplained syndrome, one that its practitioners alone are qualified to diagnose, manage, and bill for (34). Some of the modern impetus to “allow” a specific chronic fatigue syndrome arises from the various compensation and social insurance schemes operating in developed countries. Few if any insurance schemes or juridical systems will allow reimbursement or compensation for general aches, pain, and misery. Nearly all require a firm medical diagnosis, preferably one enshrined in a classification or coding system. Facing a patient who is in obvious distress and whom the physician feels is “genuine” (whatever that means), a clinician may turn with relief to a label that permits the patient to receive what the clinician feels is his or her due. In a busy clinic, we rarely trouble ourselves with conceptual or epidemiologic niceties. If the chronic fatigue syndrome did not exist, our current medical and social care systems might force us to invent it. Much the same could be said about many other symptom-based conditions discussed in this symposium, but for many reasons the chronic fatigue syndrome has become of the eye of these many storms.

TREATMENT

No single treatment for chronic fatigue or the chronic fatigue syndrome exists, and I suspect that one never will. No compelling evidence exists for the efficacy of drug therapy, including antidepressant treatment

(35). However, we are better at management than we once were. The general and rehabilitative approach to chronic illness has been shown to be effective, albeit not curative, in the chronic fatigue syndrome (35), as it is in other conditions of diverse origin. After some uncertainties, there is increasing consensus among patients and professionals alike that persistent rest as a way of managing symptoms may create more problems than it solves. In its place has come a realization that rest, activity, sleep, and exercise need to be planned coherently rather than simply in response to symptoms. If all of this sounds like common sense, then so much the better.

THE WAY FORWARD

The Mechanisms of Symptoms

Despite substantial effort on the part of the research community, we have made little progress in identifying the “cause” of the chronic fatigue syndrome. Reviews continue to express uncertainty and doubt (36–39). It is far from clear where we should even look—the muscles, the nervous or immune system, the brain, the diet, or the psyche? Further, despite the introduction of operational criteria, it remains unclear whom we should look at. A pessimist may be tempted to abandon the endeavor completely, citing, perhaps with reason, that we are really no further forward than the Victorians were when they tackled neurasthenia. However, I believe this abandonment would be premature.

Future research may shed more light by concentrating less on global attempts to find a “cause” of the chronic fatigue syndrome and more on the physiology of symptoms. Topics that may be useful include the influence of sleep, circadian rhythms, how and why well people have fatigue, the physiologic response to exercise and exercise withdrawal, and how common insults (such as certain infections or surgery) trigger fatigue.

The Sense of Effort

One theme that emerges from the literature on all of the fatigue syndromes is the possibility of a general disorder of perception that concerns both symptoms and disability. At the heart of this perception lies the sense of effort (40). For chronically fatigued patients, everyday physical and mental tasks clearly require increased effort, which is reflected in a sense of painful muscle exertion and problematic cognitive processing. Impairment is greatest when rapid cognitive processing is required (41,

42). This increased effort is the not the result of increased neuromuscular or metabolic demands (a Victorian concept), and it doesn't usually result in any substantial decline in actual muscle or cognitive performance. The result is a mismatch between a patient's evaluation of his or her physical and mental functioning and the external evidence of any consistent deficits. The basis of this disorder of effort remains speculative. It has been argued that the patient needs to devote more attention or even energy to motor and cognitive tasks, such as muscular exertion or mental concentration. Previously automatic tasks require higher levels of vigilance and thus become more effortful (40, 43).

From this fundamental problem may flow other problems identified in the chronic fatigue syndrome, such as increased symptom monitoring, decreased tolerance, and increased anxiety. These are not unique to the chronic fatigue syndrome. Patients with fibromyalgia seem abnormally sensitive to muscle-derived stimuli (44). Patients with the irritable bowel syndrome may more be sensitive to gastrointestinal discomfort from a variety of sources (45). Thus, some centrally mediated disorder of perception may underlie the experience of many syndromes with symptoms that lack clear pathophysiological explanation. This misperception may account for the frequently observed discrepancies between the intensity of symptoms and objective disability.

CONCLUSIONS

Physicists have long been at ease with the dual nature of light: It is appropriate to consider it sometimes a wave and sometimes a stream of particles. As both clinicians and researchers, we should consider a similar ambivalence about chronic fatigue and the chronic fatigue syndrome. At times, mainly in clinical practice, the chronic fatigue syndrome must be considered a discrete syndrome. The patient needs a name for his or her illness, and the clinician needs a discrete diagnosis. Similarly, service planners must have a definition to estimate need, and researchers need operational criteria to compare results. As a clinician, I could not function without the diagnosis of the chronic fatigue syndrome. But at other times, it is necessary to put aside the concept of a single syndrome. When we consider the nature of the problem in the community, we realize that boundaries may not be as discrete as they seem in the clinic. When we try to establish the cause of the problem, we may

make more progress by going back to the basic pathophysiology of chronic fatigue and related symptoms.

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