

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/236996409>

What Is Fatigue? History and Epidemiology

Chapter · January 2003

DOI: 10.7551/mitpress/2967.003.0004

CITATIONS

31

READS

14,609

2 authors:



[Susan Torres-Harding](#)

Roosevelt University

79 PUBLICATIONS 2,623 CITATIONS

[SEE PROFILE](#)



[Leonard A Jason](#)

DePaul University

1,165 PUBLICATIONS 21,817 CITATIONS

[SEE PROFILE](#)

1 What Is Fatigue? History and Epidemiology

Susan Torres-Harding and Leonard A. Jason

Fatigue is a nonspecific symptom because it can be indicative of many causes or conditions including physiological states such as sleep deprivation or excessive muscular activity; medical conditions such as chronic inflammatory conditions, bacterial or viral infections, or autoimmune illnesses; and psychiatric disorders such as major depression, anxiety disorders, and somatoform disorders (Manu, Lane, & Matthews, 1992). Fatigue may be caused by prescription medications such as antihistamines, drugs prescribed for insomnia, or chemotherapy drugs. Fatigue may also result from unhealthy lifestyles, such as frequent disruptions in the wake-sleep cycle, excessive alcohol or caffeine intake, and psychosocial stressors, or from the delayed effects of traumatic events (Manu et al., 1992). Finally, fatigue may be “unexplained,” when none of the above causes is present or the causes cannot be determined. Chronic fatigue syndrome has recently received considerable attention, and it is an illness characterized by unexplained severe, persistent, disabling fatigue (Fukuda et al., 1994).

Some describe fatigue in terms of physiological data or “objective” observations of decreasing muscle performance or decrements in work or performance. For example, fatigue has been defined as a failure to maintain a required force or output of power during sustained or repeated muscle contraction (Stokes, Cooper, & Edwards, 1988) or as time-related deterioration in the ability to perform certain mental tasks (Broadbent, 1971). In contrast to physiological fatigue, some have defined fatigue as a subjective self-reported feeling of fatigue. This feeling of fatigue is what people generally report when they seek medical treatment (Berrios, 1990). Fatigue is sometimes defined as “tiredness,” feeling tired, being fatigued, feeling weak in part of the body, tired or lacking in energy, or experiencing “everything [as] an effort” (Cope, 1992, p. 273). Physiological definitions are more easily measured, but the subjective feeling of fatigue is not directly observable (Berrios, 1990). Further, this feeling of fatigue does not always correspond directly with physiological manifestations (Berrios, 1990).

In response to its complex nature, most measures of fatigue have moved away from single questions (i.e., “Do you feel tired?”) to a more multidimensional approach. These measures assess the effect of fatigue on daily activities, mental and physical

aspects of fatigue, and other characteristics and related symptoms (Barofsky & West Legro, 1991; Chalder et al., 1993; Cope, 1992). Fatigue has also been described in terms of level of severity, level of impairment, physiological and psychological characteristics (physical vs. mental), and duration (Barofsky & West Legro, 1991; Cope, 1992). Whereas some researchers have proposed a categorical classification (i.e., absence or presence of fatigue), several research studies suggest that fatigue is best conceptualized on a continuum (Berrios, 1990; Loge et al., 1998; Pawlikowska et al., 1994; Wessely, 1998), with its variability reflecting degrees of severity (Pawlikowska et al., 1994). Despite these more recent attempts to compartmentalize fatigue, the major problem with such measures is their subjectivity.

Historical Perspectives

There has been considerable controversy over both what constitutes and what causes fatigue since the mid-nineteenth century (Wessely, 1991). By the mid-1800s, reports of upper-class women who were too weak to rise from bed were being reported frequently (Shorter, 1993). These women predominantly complained of fatigue and muscle weakness, but pain was often a prominent symptom as well. George Beard, an American neurologist, was one of the first to describe neurasthenia as a distinct clinical entity (Macmillan, 1976). The symptoms of neurasthenia included “general malaise, debility of all function, poor appetite, fugitive neuralgic pains, hysteria, insomnia, hypochondriases, disinclination for consecutive mental labor, severe and weakening attacks of headaches, and other symptoms” (Macmillan, 1976).

By 1900, neurasthenia had become the single most common diagnosis in the domain of neuropathology and psychopathology. Before 1900, however, chronic unexplained fatigue was rarely distinguished from depression (Shorter, 1993). Neurasthenia appeared to be a “wastebasket” category, used alternately as a synonym for general nervousness and evolving psychosis, as the “male” equivalent of hysteria, as a synonym for minor depression, and as a diagnosis of fatigue states in patients who were not depressed (Shorter, 1993). Physicians before 1900 had difficulty distinguishing psychogenic from neurogenic weakness. When they described “exhausted” patients, it is unclear if the problems were due to subjective perceptions of fatigue or an objective dysfunction of the muscles (Shorter, 1993). Further, when persons were described as being too exhausted to rise from bed, it was unclear whether they were simply too tired or suffered from a neurological or medical disorder (Shorter, 1993). These complaints echo contemporary descriptions of unexplained fatigue illness.

The diagnosis of neurasthenia began to fall out of use in the early 1900s, as the conceptualization of this illness shifted from physiological to psychogenic or psychological in origin (Wessely, 1991). Redefined as psychiatric, neurasthenia was less frequently diagnosed because of the stigma of psychiatric labels (Wessely, 1991).

Further, the illness was diagnosed less frequently as more working class people began to suffer from it, and it began to fade from neurological textbooks (Wessely, 1991). Within the psychiatric domain, it was subdivided into various neuroses, including obsessive-compulsive disorders, anxiety neuroses, and hysteria (Wessely, 1991). However, the diagnosis of neurasthenia is still included in the latest revision of the International Classification of Diseases, Tenth Revision (World Health Organization, 1992), and continues to be diagnosed in parts of Europe, the former Soviet Union states, and parts of Asia, where it is considered a physical disorder (Wessely, 1991).

In addition to neurasthenia, other illnesses with unexplained fatigue as a primary symptom were reported in the late nineteenth and early twentieth century. These illnesses were alternately termed effort syndrome, DaCosta's syndrome, irritable heart, disordered action of the heart, soldier's heart, and neurocirculatory asthenia. Irritable heart was noticed in the Crimean war, and later in the American Civil War (Hyams, Wignall, & Roswell, 1996). Its symptoms included diarrhea, rapid pulse, palpitation, shortness of breath, headaches, giddiness, disturbed sleep, itching skin, excessive perspiration, and indigestion. DaCosta attributed the syndrome to fevers, diarrhea, hard field service, wounds, rheumatism, scurvy, and other factors. This illness was seen as organic in origin. DaCosta believed the heart became irritable from overaction and was sustained in this state by disordered innervation (DaCosta, 1871).

During the First World War, Lewis first described effort syndrome. Its symptoms included breathlessness, cyanosis, pain, palpitation, fainting, giddiness, headaches, especially after exertion, and complaints of fatigue. Infection was considered to be a dominant factor in the etiology, as Lewis noted that approximately 32 percent of the cases he studied began with an infectious disease (Bartley & Chute, 1947). In 1918, a group of military doctors termed similar cases "neurocirculatory asthenia" (Ivy & Roth, 1944).

Initially, DaCosta's syndrome or irritable heart, Lewis's effort syndrome, and neurocirculatory asthenia were regarded as arising from anomalies of cardiac function. Over time, however, as efforts to find underlying physiological abnormalities were not successful, these illnesses began to be regarded as primarily psychosomatic or psychogenic. For example, some researchers held that these illness states were due primarily to the emotional reaction of the patient to misinterpretation of symptoms arising from effort (Ivy & Roth, 1944), fundamental nervous instability (Robey & Boas, 1918), or the effects of hyperventilation (Bartley & Chute, 1947). After World War II, a set of influential clinical studies by Paul Wood helped shift the conceptualization of effort syndromes from medical illness to psychoneuroses (Hyams, Wignall, & Roswell, 1996).

Thus, the diagnoses of neurasthenia and such illnesses as neurocirculatory asthenia fell out of favor during the early twentieth century, as they were increasingly seen as psychogenic. However, it is notable that fatigue and chronic fatigue continued to be

described as symptoms in the research literature (Bartley & Chute, 1947). Some physicians felt that chronic fatigue was due primarily to psychogenic or psychological factors; for example, Kepler (1942) described chronic fatigue as an outcome of the Western way of life, best thought of as a “psychologic” disease of the “intelligentsia.” Alvarez (1941) listed as the most common causes of chronic fatigue overwork, neuroses, postinfective neurosis, neurosis associated with arthritis or fibrositis, nervous breakdown, constitutional inadequacy, cerebral thrombosis, equivalents of insanity, and actual insanity.

Other physicians espoused a holistic approach, emphasizing the need to take into account both possible organic or physical factors, such as disease or overwork, and psychogenic or personality factors (Muncie, 1941; Wharton, 1938). For example, Wharton (1938) described patients with fatigue that was not relieved by average rest and whose symptoms appeared to be related to mental or physical depletion or both. He attributed this excessive fatigue primarily to overwork. Muncie (1941) noted that, though fatigue was among the complaints in nearly all important diseases, it was most prominent among endocrine-metabolic disorders, postinfectious states, and emotional and attitudinal states or personality maladjustment. Finally, Allen (1944) analyzed 300 cases in which the chief complaint was weakness or fatigue. Nervous conditions were considered responsible in 80 percent, and physical disorders accounted for 20 percent of the cases. These physical disorders included diabetes, heart disease, chronic infection, nephritis, anemia, and various neurological disorders.

Industrial Fatigue

Another area of research concerned the problem of industrial or occupational fatigue. In the early part of the twentieth century, attention focused on the experience and physiology of fatigue as it affected workers’ productivity. To this end, Harvard University’s Graduate School of Business set up a Fatigue Laboratory in 1927, where investigators continued research into various aspects of fatigue until 1947 (Chapman, 1990). Because worker fatigue impaired performance, a scientific and systematic study of fatigue was encouraged (Chapman, 1990). Henderson, one of the laboratory’s founders, noted that “business leaders, engineers, physiologists, and the general public” all agreed fatigue was important, but found no agreement on its definition (Chapman, 1990). The purpose of the Fatigue Laboratory was therefore to describe the physiological experiences of fatigue in everyday life, and the scope of the studies extended beyond industrial fatigue to encompass exercise physiology and medical applications (Chapman, 1990). Industrial fatigue studies included investigations into muscular exercise and fatigue, resting conditions, and adaptations to physical stress. Some studies indicated that the rest cure, or enforced complete bedrest prescription, was actually contraindicated; physical exercise was considered an important therapeutic measure (Chapman, 1990).

Ward (1941) noted in his study of 600 male and 1200 female workers that 4 percent were chronically fatigued. Many complained of feeling tired, and most also complained of back pain, loss of appetite, and insomnia, and were prone to irritability. Physical findings were increased pulse rate, low blood pressure, pallor, tremor, and weight loss. Ward concluded that anyone who works beyond 100 percent of his capacity is bound to develop fatigue-related symptoms, and overwork was a primary cause of chronic fatigue. Collier (1943) also recognized the hazards of chronic fatigue and noted that fatigue arising from overwork could lead to disease. Interestingly, although overwork was seen as a major contributor to chronic industrial fatigue, researchers such as Collier (1943) also emphasized the importance of psychological factors in industrial or occupational fatigue. Nearly all of the everyday problems of industrial fatigue, Collier noted, were psychological rather than physical (Collier, 1943).

Outbreaks of Fatigue Illnesses

During the twentieth century, several outbreaks of illnesses with fatigue of unknown etiology as a chief or principal symptom were also reported (Wessely, 1991; Levine, 1994). These unexplained fatigue illnesses were variously labeled epidemic neuromyasthenia, myalgic encephalomyelitis, Iceland disease, and atypical poliomyelitis. A major outbreak occurred in 1955 among the nursing and medical staff at the Royal Free Hospital in England (Wessely, 1991). Termed myalgic encephalomyelitis, the illness' symptoms included fatigue and muscle pain as well as other neurological signs (Shorter, 1993). Another outbreak of a severe fatigue illness, atypical poliomyelitis, occurred at the Los Angeles County Hospital in 1934 (Wessely, 1991).

Levine (1994) describes several outbreaks of epidemic neuromyasthenia, another fatigue illness of unknown etiology with fatigue as a principal symptom that often encompassed neurological symptoms and signs. Outbreaks were reported in northern England (1955) among 233 males and females; in a private medical facility near Washington, D.C. (1953); and in Ridgefield, Connecticut (1955–1956), at a small medical research facility and neighboring community. Finally, in Lake Tahoe, Nevada, and the surrounding communities (1984–1986), an outbreak of 184 cases of a severe fatigue illness occurred. The symptoms of the Lake Tahoe outbreak included prolonged fatigue, abrupt onset of symptoms, severe pain, and prominent cognitive disorder (Levine, 1994).

Contemporary Investigations into Fatigue

Interest in fatigue was renewed in the late 1980s with the emergence of chronic Epstein-Barr virus syndrome. This syndrome explained chronic fatigue as a persistent viral illness caused by the same pathogen responsible for acute mononucleosis (Friedberg & Jason, 1998). Later renamed chronic fatigue syndrome, or CFS (Wessely,

1998), the syndrome's criteria were developed in 1988 (Holmes et al., 1988), and later refined in 1994 (Fukuda et al., 1994). The 1994 criteria for CFS include severe, disabling fatigue lasting 6 months or more. The illness also requires four of eight additional symptoms: sore throat, headaches, lymph node tenderness or pain, joint pain, muscle pain, unrefreshing sleep, postexertional malaise, and memory or concentration difficulties. Finally, for a diagnosis of CFS, the fatigue must be "unexplained," that is, not better accounted for by another medical or psychiatric condition (Fukuda et al., 1994).

Unexplained chronic fatigue has also been diagnosed as myalgic encephalomyelitis, ME (Wessely, 1991). The criteria for ME include fatigue after minimal exertion and delayed recovery of muscle power after exertion; symptoms of circulatory impairment; and central nervous system involvement (cerebral problems). These symptoms often have a chronic, fluctuating course (Ramsay, 1988).

Fatigue has been a frequent reason for visits to physicians (Nelson et al., 1987), and the chief complaint in 4 to 9 percent of all visits to a family practitioner or internist (Manu, Lane, & Matthews, 1992). Studies of people presenting with fatigue in primary care settings show an estimated 7.6 to 32 percent of these patients have fatigue as either a symptom or chief complaint (Cathebras et al., 1992; Fuhrer & Wessely, 1995; Kroenke, Wood, Mangelsdorff, Meier, & Powell, 1988). Further, excessive fatigue affects a significant proportion of the general population. It has been noted to be a common symptom in both community-based studies (Cope, 1992; Pawlikowska et al., 1994) and primary care and hospital-based studies of fatigue prevalence (Fuhrer & Wessely, 1995; Cope, 1992). Fatigue can also have a powerful, adverse effect on quality of life (Nelson et al., 1987).

The problem of chronic fatigue has also received considerable attention. Typically defined as excessive fatigue lasting more than 6 months (Fukuda et al., 1994), chronic fatigue is considered more severe and disabling than acute fatigue because of its persistent, chronic course (Fukuda et al., 1994). Chronic fatigue is estimated to occur in approximately 4 to 5 percent of the general population (Jason, Jordan et al., 1999).

Gender and Fatigue

Many studies have examined the role of gender in fatigue. Some studies have found gender differences in fatigue, with women more likely to report having both fatigue and chronic fatigue (Chen, 1986; Nelson et al., 1987; Loge et al., 1998; Nisenbaum et al., 1998; Jason, Jordan et al., 1988). Some researchers have also found that women tend to report more severe fatigue (Chen, 1986; Kroenke et al., 1988; Loge et al., 1998; Jason, Jordan et al., 1998; Nisenbaum et al., 1998; Pawlikowska et al., 1994). Further, women are also more than twice as likely to seek medical help for their fatigue (Cope, 1992). For example, two-thirds of the people in one study who presented with fatigue in a primary care practice were women (Nelson et al., 1987). However, some primary

care and hospital studies have found no statistically significant gender differences in fatigue (Cathebras et al., 1995; Kirk, Douglas, Nelson, Jaffee, & Lopez, 1990).

Ethnicity and Fatigue

Relatively few studies have examined fatigue levels among different ethnic groups (Richman, Flaherty, & Rospenda, 1994). Cathebras and associates (1995), in examining English-speaking and French-speaking Canadians, found an ethnic difference in reported rates of fatigue, with French-speaking Canadians reporting more fatigue. Buchwald and others (1996), however, found no ethnic differences in their study of white and “nonwhite” (African American, Asian American, American Indian, and Latino) people attending a university health center. Similarly, Nisenbaum and coworkers (1998), in a representative sample of people living within the San Francisco urban area, failed to find any ethnic differences in reported levels of fatigue. However, Steele and associates (1998) reported higher levels of fatigue among Native Americans. Finally, Song, Jason, and Taylor (1999) found that the mean fatigue severity scores were significantly higher for African Americans and Latinos than for Caucasians.

Although these community-based studies seem to point to some ethnic group differences, the problem of fatigue in multiethnic populations continues to be understudied. Selection bias may play a part in the lack of ethnic minority studies, as many primary care or hospital-based studies report few ethnic minority group members among their sample. People of color may have poorer access to quality health care, because of their disproportionate representation in lower socioeconomic populations (Richman, Flaherty, & Rospenda, 1994). This relative absence of people of color in research is especially disconcerting since some studies suggest they may be at higher risk for severe fatigue (Song, Jason, & Taylor, 1999), and inappropriate conclusions about the etiology of this illness may be drawn from a highly select, ethnically homogeneous population. Community-based studies hold more promise of representing persons of color, and sampling from ethnically diverse populations may help to elucidate the prevalence and experience of fatigue in these traditionally understudied groups.

Physical versus Psychological Causes of Fatigue

The debate as to whether fatigue has primarily a physical or psychological etiology continues in contemporary investigations. Some researchers have distinguished between central and peripheral fatigue. Peripheral fatigue is defined as failure to sustain force or power output because of “failure in neuromuscular transmission, sarcolemmal excitation, or excitation-contraction coupling,” implying neuromuscular dysfunction outside of the central nervous system, or CNS (Edwards, Newham, & Peters, 1991; Swain, 2000). In contrast, central fatigue is defined as resulting from failure to achieve and maintain the recruitment of high-threshold motor

units (Edwards, Newham, & Peters, 1991), implicating dysfunction in CNS neurotransmitter pathways (Swain, 2000). However, the contributions of neither peripheral fatigue nor central fatigue to overall subjective reports of fatigue is well understood.

Clinical studies tend to focus on self-reported feeling of fatigue (Swain, 2000). Such studies often find a mixed presentation of both physical and psychological factors in unexplained chronic fatigue (Hall et al., 1994). Elevated rates of psychiatric comorbidity or indicators of psychological disorder have been found among chronic fatigue patients in primary care settings (Cathebras et al., 1995; Manu et al., 1989; McDonald, David, Pelosi, & Mann, 1993). Community-based studies have also found that persons suffering from chronic fatigue were more likely to have psychiatric symptoms or be diagnosed with psychiatric disorders (Lawrie et al., 1997; Pawlikowska et al., 1994). Somatic symptoms often occur together with self-reported fatigue as well. Manu and associates (1989) found that the most frequent somatic symptoms in fatigue patients were pain in extremities, joints, chest, and other parts of the body; shortness of breath; blurred vision; muscle weakness; and sexual indifference (Manu et al., 1989). Hartz and coworkers (1998) noted that the number of symptoms was strongly associated with the severity of fatigue, the response of fatigue to mental and physical activity, and the following participant characteristics: a greater frequency of sinus and respiratory infections, a higher frequency of migraines, a greater number of somatoform symptoms not included as criteria for CFS, and abstinence from alcohol (Hartz et al., 1998). Nisenbaum and associates (1998) found the most common symptoms experienced by fatigued persons were sleep problems, general weakness, muscle aches and pain, difficulty thinking or concentrating, depression, and unusual fatigue after exertion. These findings suggest that other somatic symptoms are likely to arise as unexplained severe fatigue persists (Nisenbaum et al., 1998).

Factor analytic studies tend to find multiple factors or clusters of fatigue-related symptoms. Ray, Weir, Cullen, and Phillips (1992) analyzed a list of symptoms in 208 patients with postviral fatigue and found four factors: emotional distress, fatigue, somatic symptoms, and cognitive difficulty. Hall, Sanders, and Replogle (1998), in a sample of 197 primary care patients, performed a factor analysis using 34 reported symptoms. In this investigation, four clusters of symptoms emerged: organic symptoms, anxiety, depression, and mixed-anxiety depression. Nisenbaum and associates (1998) also conducted a factor analysis of 30 symptoms experienced by people who were fatigued for 6 months or more, finding fatigue/mood/cognition, flu-type, and visual problem factors (Nisenbaum et al., 1998). Finally, Jason and coworkers (2002) factor analyzed fatigue-related symptoms reported by 780 persons with chronic fatigue and found four factors: lack of energy, physical exertion, cognitive problems, and fatigue and rest.

As Berrios (1990) noted, it is unclear whether the feeling of fatigue represents a primary state or a composite of symptoms that may vary depending on the etiology of the medical condition. These studies suggest that subjective unexplained fatigue

may not always represent strictly “psychological” or “physical” etiologies; there may be separate physiological and psychological contributions to the experience of fatigue. This echoes Bartley and Chute’s recommendation in 1947, that fatigue and chronic fatigue research should examine the relative importance of multiple physical and psychological contributions (Bartley & Chute, 1947) to the experience of overall fatigue.

Unexplained Fatigue in Chronic Fatigue Syndrome

Only a small minority of patients presenting with chronic or severe fatigue are actually diagnosed with chronic fatigue syndrome. The prevalence of this disorder has been estimated at 0.24 percent (Reeves, 1999) to 0.4 percent (Jason et al., 1999) in community-based studies, and 2.6 percent of patients in primary care (Wessely, Chalder et al., 1997). As fatigue is the defining symptom of this illness, all persons diagnosed with chronic fatigue syndrome have experienced severe and disabling fatigue for 6 months or more (Fukuda et al., 1994). The effects of this chronic, unexplained fatigue appear to differ from individual to individual, with some persons experiencing only mild impairment, while others experience severe or very severe limitations (Carrico, Jason, Torres-Harding, & Witter, 2004; Cox & Findley, 2000). The fatigue in CFS can lead to a markedly higher degree of impairment than is found other chronically ill populations (Anderson & Ferrans, 1997).

As an illness of unexplained fatigue, CFS is diagnosed only when other fatigue-causing conditions are ruled out as the primary source of the fatigue. Because the fatigue is designated as “unexplained,” some have proposed psychiatric explanations for the illness, while others propose several physiological hypotheses to explain the illness process and its resulting symptomatology. Regarding physiological findings, Clauw and Chrousos (1997) suggest that individuals who develop CFS might be genetically predisposed to develop this condition. In support of this, Torres-Harding and Jason (2003) found that persons with CFS were significantly more likely to report a family history of metabolic disorders than a control group. Recent twin studies of complex genetic and environmental relationships between psychological distress, fatigue, and immune system functioning suggest the need to acknowledge the increasing importance of the individual’s genotype (Hickie, Bennett, Lloyd, Heath, & Martin, 1999). Clauw and Chrousos further posit that susceptible individuals might evidence a number of organ-specific illnesses before progressing to CFS. Supportive data support this thesis, showing CFS patients have had significantly more upper respiratory tract infections, lethargy, and vertigo than controls (Hamilton et al., 2001).

Clauw and Chrousos also suggest that once CFS develops, either abruptly or slowly through viral infections or emotional stressors, the human stress response is blunted, along with blunting of the hypothalamic-pituitary axis and autonomic nervous system instability. Symptom heterogeneity might be due to different axes of the stress

response, either independently or concurrently functioning in aberrantly. Patients with CFS experience blunted biological stress response, and a low corticotrophin-releasing hormone (CRH) state is exacerbated if exercise further reduces cortisol levels; this postexercise adrenal insufficiency could be responsible for the patients' severe post-exertional fatigue. One strength of such a biopsychosocial understanding of CFS is that it may bridge the theoretical gap between mind versus body explanations of these illnesses.

Fatigue in Chronic Disease

In addition to unexplained fatigue, the occurrence of fatigue in specific medical diseases has also been investigated. Fatigue has come to be recognized as a serious symptom of many illnesses that can significantly impair a person's functioning and have a negative impact on quality of life in many chronic illnesses, including after cancer treatment (Bartsch, Weis, & Moser, 2003; Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Smets et al., 1993), systemic lupus erythematosus (SLE) (Jacobson, Gange, Rose, & Graham, 1997), multiple sclerosis (Schwid, Covington, Segal, & Goodman, 2002), human immunodeficiency virus (HIV) infection, viral and cholestatic liver diseases, and rheumatoid arthritis (Swain, 2000).

However, understanding fatigue in chronic medical disease continues to prove difficult. Even when fatigue is considered a primary or a common symptom, such as in multiple sclerosis or SLE, fatigue often does not correlate with disease status or physiological findings (Schwid, Covington, Segal, & Goodman, 2002; Krupp et al., 1990; Wang et al., 1998; Omdal et al., 2003). Despite the recognition that fatigue is an integral component of chronic disease, its etiology in many chronic illnesses is not well understood, although some have proposed it is mainly of central origin (Swain, 2000). Swain (2000) proposes that corticotropin-releasing hormone and chronic stress, cytokines and immune activation, central neurotransmitter pathways, and mood disorders such as depression are possible factors contributing to fatigue in chronic diseases. Further, different chronic illnesses may vary in the relative contributions of peripheral and central fatigue to the overall experience of fatigue (Swain, 2000). Finally, other factors such as stress, sleep disturbance, distress of other somatic symptoms, and personality traits have been reported to contribute to the subjective experience of fatigue in chronic disease (Berger, 2003; Irvine et al., 1994; Schwid, Covington, Segal, & Goodman, 2002).

Summary

The problem of excessive or unexplained fatigue has been common from the middle of the nineteenth century to the present day. Today, both unexplained fatigue and

fatigue occurring as a symptom of illness are recognized as serious symptoms that can severely limit physical functioning and have a negative impact on quality of life. Research supports the involvement of multiple dimensions, with physiological, psychological, and psychosocial factors contributing to the experience of fatigue. Fatigue often occurs in conjunction with other somatic and psychiatric symptoms.

The relationship between physiological fatigue or disease states and the feeling of fatigue remains poorly understood, partly because fatigue is difficult to define and measure. Unfortunately, theories on the nature of fatigue from the last century are closely echoed by contemporary views, with little progress made in understanding this symptom. A recurring theme in research, however, is the need for a biopsychosocial approach, incorporating physiological, psychological, and psychosocial factors, in understanding the experience of fatigue. Continued research into the factors contributing to fatigue may help elucidate this complex symptom.

Acknowledgment

The authors appreciate the financial support of NIAID and grant number AI49720.

References

- Anderson, J. S., & Ferrans, C. E. (1997). The quality of life of persons with chronic fatigue syndrome. *Journal of Nervous and Mental Disease*, 185, 359–367.
- Allen, F. N. (1944). The differential diagnosis of weakness and fatigue. *New England Journal of Medicine*, 231, 414–418.
- Alvarez, W. C. (1941). What is the matter with the patient who is chronically tired? *Journal of Missouri Medical Association*, 38, 365–368.
- Barofsky, I., & West Legro, M. (1991). Definition and measurement of fatigue. *Reviews of Infectious Diseases*, 13, S94–S97.
- Bartley, S. H., & Chute, E. (1947). *Fatigue and Impairment in Man*. New York: McGraw-Hill.
- Bartsch, H. H., Weis, J., & Moser, M. T. (2003). Cancer-related fatigue in patients attending oncological rehabilitation programs: prevalence, patterns, and predictors. *Onkologie*, 26(1), 51–57.
- Berger, A. (2003). Treating fatigue in cancer patients. *Oncologist*, 8(Suppl 1), 10–14.
- Berrios, G. E. (1990). Feelings of fatigue and psychopathology: a conceptual history. *Comprehensive Psychiatry*, 31(2), 140–151.
- Broadbent, D. (1971). *Decision and Stress*. London: Academic Press.
- Buchwald, D., Manson, S. M., Pearlman, T., Umali, J., & Kith, P. (1996). Race and ethnicity in patients with chronic fatigue. *Journal of Chronic Fatigue Syndrome*, 2(1), 1996.

- Carrico, A. W., Jason, L. A., Torres-Harding, S. R., & Witter, E. A. (2004). Disability in chronic fatigue syndrome and idiopathic chronic fatigue. *Review of Disability Studies: An International Journal*, 1, 79–88.
- Cathebras, P. J., Robbins, J. M., Kirmayer, L. J., & Hayton, B. C. (1992). Fatigue in primary care: prevalence, psychiatric comorbidity, illness behavior, and outcome. *Journal of General Internal Medicine*, 7, 276–286.
- Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., & Wallace, E. P. (1993). Development of a fatigue scale. *Journal of Psychosomatic Research*, 37(2), 147–153.
- Chapman, C. B. (1990). The long reach of Harvard's Fatigue Laboratory, 1926–1947. *Perspectives in Biology and Medicine*, 34(1), 17–33.
- Chen, M. (1986). The epidemiology of self-perceived fatigue among adults. *Preventive Medicine*, 15, 74–81.
- Clauw, D. J., & Chrousos, G. P. (1997). Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *Neuroimmunomodulation*, 4, 134–153.
- Collier, H. E. (1943). *Outlines of Industrial Medical Practice*. Baltimore: Williams & Wilkins Company.
- Cope, H. (1992). Fatigue: a non-specific complaint? *International Review of Psychiatry*, 4, 273–280.
- Cox, D. L., & Findley, L. J. (2000). Severe and very severe patients with chronic fatigue syndrome: perceived outcome following an inpatient program. *Journal of Chronic Fatigue Syndrome*, 7(3), 33–47.
- DaCosta, J. M. (1871). On irritable heart: a clinical study of a form of functional cardiac disorder and its consequences. *American Journal of Medical Science*, 61, 17–52.
- Edwards, R. H. T., Newham, D. J., & Peters, T. J. (1991). Muscle biochemistry and pathophysiology in postviral fatigue syndrome. *British Medical Bulletin*, 47(4), 826–837.
- Friedberg, F., & Jason, L. A. (1998). *Understanding Chronic Fatigue Syndrome*. Washington, DC: American Psychological Association.
- Fuhrer, R., & Wessely, S. (1995). The epidemiology of fatigue and depression: a French primary care study. *Psychological Medicine*, 25, 895–905.
- Fukuda, K., Straus, S., Hickie, I., Sharpe, M. C., Dobbins, J. G., & Komaroff, A., & The International Chronic Fatigue Syndrome Study Group (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine*, 121, 953–959.
- Hall, D. G., Sanders, S. D., & Replogle, W. H. (1994). Fatigue: a new approach to an old problem. *Journal of the Mississippi State Medical Association*, 35, 155–160.
- Hamilton, W. T., Hall, G. H., & Pound, A. P. (2001). Frequency of attendance in general practice and symptoms before development of chronic fatigue syndrome: a case-control study. *British Journal of General Practice*, 51, 553–558.

- Hartz, A. J., Kuhn, E. M., & Levine, P. (1998). Characteristics of fatigued persons associated with features of chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome*, 4(3), 71–97.
- Hickie, I., Bennett, B., Lloyd, A., Heath, A., & Martin, N. (1999). Complex genetic and environmental relationships between psychological distress, fatigue and immune functioning: a twin study. *Psychological Medicine*, 29, 267–277.
- Holmes, G. P., Kaplan, J. E., Gantz, N. M., et al. (1988). Chronic fatigue syndrome: a working case definition. *Annals of Internal Medicine*, 108, 387–389.
- Hyams, K. C., Wignall, F. S., & Roswell, R. (1996). War syndromes and their evaluation: from the US Civil War to the Persian Gulf War. *Annals of Internal Medicine*, 125, 398–405.
- Irvine, D., Vincent, L., Graydon, J. E., Bubela, N., & Thompson, L. (1994). The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. A comparison with the fatigue experienced by healthy individuals. *Cancer Nursing*, 17(5), 367–378.
- Ivy, A. C., & Roth, J. A. (1944). A review of neurocirculatory asthenia, cardiovascular neurosis, effort syndrome, or DaCosta's syndrome. *Quarterly Bulletin of Northwestern University*, 18, 112–124.
- Jacobson, D. L., Gange, S. J., Rose, N. R., & Graham, N. M. (1997). Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clinical Immunology and Immunopathology*, 84(3), 223–243.
- Jason, L. A., Jordan, K. M., Richman, J. A., Rademaker, A. W., Huang, C., McCready, W., Shlaes, J., King, C. P., Landis, D., Torres, S., Haney-Davis, T., & Frankenberry, E. L. (1999). A community-based study of prolonged and chronic fatigue. *Journal of Health Psychology*, 4, 9–26.
- Jason, L. A., Richman, J. A., Rademaker, A. W., Jordan, K. M., Plioplys, A. V., Taylor, R. R., McCready, W., Huang, C. F., & Plioplys, S. (1999). A community-based study of chronic fatigue syndrome. *Archives of Internal Medicine*, 159(18), 2129–2137.
- Jason, L. A., Taylor, R. R., Kennedy, C. L., Jordan, K., Huang, C. F., Torres-Harding, S., Song, S., & Johnson, D. (2002). A factor analysis of chronic fatigue symptoms in a community-based sample. *Social Psychiatry and Psychiatric Epidemiology*, 37, 183–189.
- Kepler, E. J. (1942). Chronic fatigue. *Proceedings of the Staff Meetings, Mayo Clinic*, 17, 340–344.
- Kirk, J., Douglass, R., Nelson, E., Jaffee, J., & Lopez, A. (1990). Chief complaint of chronic fatigue: a prospective study. *Journal of Family Practice*, 30(1), 33–41.
- Kroenke, K., & Mangelsdorff, A. D. (1989). Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. *The American Journal of Medicine*, 86, 262–266.
- Kroenke, K., Wood, D. R., Mangelsdorff, A. D., Meier, N. J., & Powell, J. B. (1988). Chronic fatigue in primary care: prevalence, patient characteristics, and outcome. *Journal of the American Medical Association*, 260(7), 929–934.
- Krupp, L. B., & Christodoulou, C. (2001). Fatigue in multiple sclerosis. *Current Neurology and Neuroscience Reports*, 1(3), 294–298.

- Lawrie, S. M., Manders, D. N., Geddes, J. R., & Pelosi, A. J. (1997). A population-based incidence study of chronic fatigue. *Psychological Medicine*, 27, 343–353.
- Levine, P. H. (1994). Epidemic neuromyasthenia and chronic fatigue syndrome: epidemiological importance of a cluster definition. *Clinical Infectious Diseases*, 18(Suppl 1), S16–S20.
- Loge, J. H., Ekeberg, O., & Kaasa, S. (1998). Fatigue in the general Norwegian population: normative data and associations. *Journal of Psychosomatic Research*, 45(1), 53–65.
- Macmillan, M. B. (1976). Beard's concept of neurasthenia and Freud's concept of the actual neuroses. *Journal of the History of the Behavioral Sciences*, 12(4), 376–390.
- Manu, P., Lane, T. J., & Matthews, D. A. (1992). Chronic fatigue syndromes in clinical practice. *Psychotherapy and Psychosomatics*, 58, 60–68.
- Manu, P., Matthews, D. A., Lane, T. J., Tennen, H., Hesselbrock, V., Mendola, R., & Affleck, G. (1989). Depression among patients with a chief complaint of chronic fatigue. *Journal of Affective Disorders*, 17, 165–172.
- McDonald, E., David, A. S., Pelosi, A. J., & Mann, A. H. (1993). Chronic fatigue in primary care attenders. *Psychological Medicine*, 23(4), 987–998.
- Muncie, W. (1941). Chronic fatigue. *Psychosomatic Medicine*, 3, 277–285.
- Nelson, E., Kirk, J., McHugo, G., Douglass, R., Ohler, J., Wasson, J., & Zubkoff, M. (1987). Chief complaint fatigue: a longitudinal study from the patient's perspective. *Family Practice Research Journal*, 6(4), 175–188.
- Nisenbaum, R., Reyes, M., Mawle, A. C., & Reeves, W. (1998). Factor analysis of unexplained severe fatigue and interrelated symptoms. *American Journal of Epidemiology*, 148(1), 72–77.
- Omdal, R., Waterloo, K., Koldingsnes, W., Husby, G., & Mellgren, S. I. (2003). Fatigue in patients with systemic lupus erythematosus: the psychosocial aspects. *The Journal of Rheumatology*, 30(2), 283–287.
- Pawlikowska, T., Chalder, T., Hirsch, S. R., Wallace, P., Wright, D. J. M., & Wessely, S. C. (1994). Population based study of fatigue and psychological distress. *British Medical Journal*, 308, 763–766.
- Ramsay M. A. (1988). *Myalgic encephalomyelitis and postviral fatigue states: the saga of Royal Free Disease*, 2nd ed. Aldershot, Hampshire, UK: Gower.
- Ray, C., Weir, R. C., Cullen, S., & Phillips, S. (1992). Illness perception and symptom components in chronic fatigue syndrome. *Journal of Psychosomatic Research*, 36(3), 243–256.
- Reeves, W. C. (1999). Transcript of U.S. Chronic Fatigue Syndrome Coordinating Committee of April 21–22, 1999, Bethesda, MD. Available at <http://www.cais.net/cfs-news/cfsc-9904.txt>. Accessed August 10, 1999.
- Richman, J. A., Flaherty, J. A., & Rospenda, K. M. (1994). Chronic fatigue syndrome: Have flawed assumptions been derived from treatment-based studies? *American Journal of Public Health*, 84(2), 282–284.

- Robey, W. H., & Boas, E. P. (1918). Neurocirculatory asthenia. *Journal of the American Medical Association*, 71, 525–529.
- Schwid, S. R., Covington, M., Segal, B. M., & Goodman, A. D. (2002). Fatigue in multiple sclerosis: current understanding and future directions. *Journal of Rehabilitation Research and Development*, 39(2), 211–224.
- Shorter, E. (1993). Chronic fatigue in historical perspective. In *Chronic Fatigue Syndrome: CIBA Foundation Symposium*. G. R. Bock & J. Whelan, eds. Pp. 6–22. Chichester, Engl.: John Wiley & Sons.
- Smets, E. M. A., Garssen, B., Schuster-Uitterhoeve, A. L. J., & de Haes, J. C. J. M. (1993). Fatigue in cancer patients. *British Journal of Cancer*, 68(2), 220–224.
- Song, S., Jason, L. A., & Taylor, R. R. (1999). The relationship between ethnicity and fatigue in a community-based sample. *Journal of Gender, Culture, and Health*, 4(4), 255–268.
- Steele, L., Dobbins, J. G., Fukuda, K., Reyes, M., Randall, B., Koppelman, M., & Reeves, W. C. (1998). The epidemiology of chronic fatigue in San Francisco. *American Journal of Medicine*, 105, 835–905.
- Stokes, M. J., Cooper, R. G., & Edwards, R. H. T. (1988). Normal muscle strength and fatigability in patients with effort syndromes. *British Medical Journal*, 297, 1014–1016.
- Swain, M. G. (2000). Fatigue in chronic disease. *Clinical Science*, 99, 1–8.
- Torres-Harding, S. R., & Jason, L. A. (2003). “Family medical history of persons with chronic fatigue syndrome.” Paper presented at the meeting of the American Association of Chronic Fatigue Syndrome. Chantilly, Virginia.
- Wang, B., Gladman, D. D., & Urowitz, M. B. (1998). Fatigue in lupus is not correlated with disease activity. *The Journal of Rheumatology*, 25, 892–895.
- Ward, R. V. (1941). Chronic fatigue symptoms among industrial workers. *Canadian Public Health Journal*, 32, 464–467.
- Wessely, S. (1991). History of postviral fatigue syndrome. *British Medical Bulletin*, 47(4), 919–941.
- Wessely, S. (1998). The epidemiology of chronic fatigue syndrome. *Epidemiologia e Psichiatria Sociale*, 7(1), 10–24.
- Wessely, S., Chalder, T., Hirsch, S., Wallace, P., & Wright, D. (1997). The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. *American Journal of Public Health*, 87, 1449–1455.
- Wharton, G. K. (1938). The fatigue syndrome. *Canadian Medical Association Journal*, 38, 339–342.
- World Health Organization (1992). *International Classification of Diseases and Related Health Problems*, Tenth Revision. Albany, NY: WHO Publications Center USA.