a therapeutic alliance, the goal of which is to spare patients expensive and fruitless diagnostic workups and steer them toward effective therapy.

EPIDEMIOLOGY AND GLOBAL CONSIDERATIONS

Variability in the definitions of fatigue and the survey instruments used in different studies makes it difficult to arrive at precise figures about the global burden of fatigue. The point prevalence of fatigue was 6.7% and the lifetime prevalence was 25% in a large National Institute of Mental Health survey of the U.S. general population. In primary care clinics in Europe and the United States, between 10 and 25% of patients surveyed endorsed symptoms of prolonged (present for >1 month) or chronic (present for >6 months) fatigue, but fatigue was the primary reason for seeking medical attention in only a minority of patients. In a community survey of women in India, 12% reported chronic fatigue. By contrast, the prevalence of chronic fatigue syndrome, as defined by the U.S. Centers for Disease Control and Prevention, is low (Chap. 464e).

DIFFERENTIAL DIAGNOSIS

Psychiatric Disease Fatigue is a common somatic manifestation of many major psychiatric syndromes, including depression, anxiety, and somatoform disorders. Psychiatric symptoms are reported in more than three-quarters of patients with unexplained chronic fatigue. Even in patients with systemic or neurologic syndromes in which fatigue is independently recognized as a manifestation of disease, comorbid psychiatric symptoms or disease may still be an important source of interaction.

Neurologic Disease Patients complaining of fatigue often say they feel weak, but upon careful examination, objective muscle weakness is rarely discernible. If found, muscle weakness must then be localized to the central nervous system, peripheral nervous system, neuromuscular junction, or muscle and the appropriate follow-up studies obtained (Chap. 30). *Fatigability* of muscle power is a cardinal manifestation of some neuromuscular disorders such as myasthenia gravis and can be distinguished from *fatigue* by finding clinically apparent diminution of the amount of force that a muscle generates upon repeated contraction (Chap. 461). Fatigue is one of the most common and bothersome symptoms reported in multiple sclerosis (MS) (Chap. 458), affecting nearly 90% of patients; fatigue in MS can persist between MS attacks and does not necessarily correlate with magnetic resonance imaging (MRI) disease activity. Fatigue is also increasingly identified as a troublesome feature of many other neurodegenerative diseases, including Parkinson's disease, central dysautonomias, and amyotrophic lateral sclerosis. Poststroke fatigue is a well-described but poorly understood entity with a widely varying prevalence. Episodic fatigue can be a premonitory symptom of migraine. Fatigue is also a frequent result of traumatic brain injury, often occurring in association with depression and sleep disorders.

Sleep Disorders Obstructive sleep apnea is an important cause of excessive daytime sleepiness in association with fatigue and should be investigated using overnight polysomnography, particularly in those with prominent snoring, obesity, or other predictors of obstructive sleep apnea (Chap. 319). Whether the cumulative sleep deprivation that is common in modern society contributes to clinically apparent fatigue is not known (Chap. 38).

Endocrine Disorders Fatigue, sometimes in association with true muscle weakness, can be a heralding symptom of hypothyroidism, particularly in the context of hair loss, dry skin, cold intolerance, constipation, and weight gain. Fatigue in association with heat intolerance, sweating, and palpitations is typical of hyperthyroidism. Adrenal insufficiency can also manifest with unexplained fatigue as a primary or prominent symptom, often in association with anorexia, weight loss, nausea, myalgias, and arthralgias; hyponatremia and hyperkalemia may be present at time of diagnosis. Mild hypercalcemia can cause fatigue, which may be relatively vague, whereas severe hypercalcemia can lead to lethargy, stupor, and coma. Both hypoglycemia and hyperglycemia can cause lethargy, often in association with confusion; chronic diabetes, particularly type 1 diabetes, is also associated with fatigue independent of glucose levels. Fatigue may also accompany Cushing's disease, hypoaldosteronism, and hypogonadism.

Liver and Kidney Disease Both chronic liver failure and chronic kidney disease can cause fatigue. Over 80% of hemodialysis patients complain of fatigue, which makes this one of the most common patient-reported symptoms in chronic kidney disease.

Obesity Obesity is associated with fatigue and sleepiness independent of the presence of obstructive sleep apnea. Obese patients undergoing bariatric surgery experience improvement in daytime sleepiness sooner than would be expected if the improvement were solely the result of weight loss and resolution of sleep apnea. A number of other factors common in obese patients are likely contributors as well, including depression, physical inactivity, and diabetes.

Malnutrition Although fatigue can be a presenting feature of malnutrition, nutritional status may also be an important comorbidity and contributor to fatigue in other chronic illnesses, including cancer-associated fatigue.

Infection Both acute and chronic infections commonly lead to fatigue as part of the broader infectious syndrome. Evaluation for undiagnosed infection as the cause of unexplained fatigue, and particularly prolonged or chronic fatigue, should be guided by the history, physical examination, and infectious risk factors, with particular attention to risk for tuberculosis, HIV, chronic hepatitis B and C, and endocarditis. Infectious mononucleosis may cause prolonged fatigue that persists for weeks to months following the acute illness, but infection with the Epstein-Barr virus is only very rarely the cause of unexplained chronic fatigue.

Drugs Many medications, drug use, drug withdrawal, and chronic alcohol use can all lead to fatigue. Medications that are more likely to be causative in this context include antidepressants, antipsychotics, anxiolytics, opiates, antispasticity agents, antiseizure agents, and beta blockers.

Cardiovascular and Pulmonary Fatigue is one of the most taxing patient-reported symptoms of congestive heart failure and chronic obstructive pulmonary disease and negatively affects quality of life.

Malignancy Fatigue, particularly in association with unexplained unintended weight loss, can be a sign of occult malignancy, but this is only rarely identified as causative in patients with unexplained chronic fatigue in the absence of other telltale signs or symptoms. Cancer-related fatigue is experienced by 40% of patients at time of diagnosis and greater than 80% of patients later in the disease course.

Hematologic Chronic or progressive anemia may present with fatigue, sometimes in association with exertional tachycardia and breathlessness. Anemia may also contribute to fatigue in chronic illness. Low serum ferritin in the absence of anemia may also cause fatigue that is reversible with iron replacement.

Systemic Inflammatory/Rheumatologic Disorders Fatigue is a prominent complaint in many chronic inflammatory disorders, including systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis, inflammatory bowel disease, antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, sarcoidosis, and Sjögren's syndrome, but is not usually an isolated symptom.

Pregnancy Fatigue is very commonly reported by women during all stages of pregnancy and postpartum.

Disorders of Unclear Cause Chronic fatigue syndrome (Chap. 464e) and fibromyalgia (Chap. 396) incorporate chronic fatigue as part of the syndromic definition when present in association with a number of other inclusion and exclusion criteria, as discussed in detail in