Chronic fatigue syndrome (named by some as myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS]) frustrates many physicians. That is understandable because there are no diagnostic tests or proven treatments. Some physicians even insist that the illness has no biological basis. Patients who seek help from such physicians are unlikely to have a satisfying therapeutic experience.

Fortunately, ME/CFS has recently received some welcome attention from the Institute of Medicine (IOM), Agency for Healthcare Research and Quality (AHRQ), and National Institutes of Health (NIH). Four articles in Annals address their findings (1–4). I will recap their answers to important questions.

**How Prevalent and Important Is the Illness?**

The IOM estimates that 836,000 to 2.5 million Americans have ME/CFS (5). The direct and indirect economic costs of the illness to society are estimated to be between $17 billion and $24 billion annually.

**Is ME/CFS Real?**

According to the most widely used case definition (6), the illness is characterized exclusively by symptoms; therefore, physicians have understandably wondered whether there are “real” underlying biological abnormalities. The IOM, AHRQ, and NIH panels concluded that there are such biological abnormalities. After evaluating thousands of published articles, the IOM committee stated that “ME/CFS is a serious, chronic, complex systemic disease that often can profoundly affect the lives of patients” (5). Summarizing the committee’s deliberations, Ganiats (1) said that the illness “is not, as many clinicians believe, a psychological problem,” while emphasizing that psychiatric comorbid conditions occur in some patients with ME/CFS and need to be diagnosed and treated.

The IOM committee concluded that there is evidence of various neurologic abnormalities in patients with ME/CFS (5). Formal studies of cognition show slowed information processing, potentially related to problems with white matter integrity. A positron emission tomography study demonstrated neuroinflammation (activated microglia or astrocytes) (6), functional magnetic resonance imaging studies found distinctive abnormalities when patients were challenged with working memory tasks, and the NIH report found “strong evidence of neurotransmitter signaling disruption.” Studies summarized in the IOM report showed that some patients had reduced overnight cortisol, 24-hour urinary cortisol, and adrenocorticotropic hormone levels compared with healthy control participants, suggesting a secondary (brain) rather than a primary (adrenal) cause of reduced cortisol production. Many patients have orthostatic intolerance, manifested by objective heart rate and blood pressure abnormalities during standing or head-up tilt testing.

The IOM report also concluded that several immunologic abnormalities have been demonstrated in ME/CFS. Patients may have poor natural killer cell cytotoxicity that correlates with illness severity, although the IOM report noted that this abnormality was not specific to ME/CFS. There may be increased cytokine levels in the blood (or increased production of cytokines by leukocytes in the culture), suggesting a state of immune activation, although not all studies agreed on this point. A recently published study—the largest of its type (298 case participants, 348 healthy control participants, and 51 cytokines measured in each blood sample)—found strikingly increased cytokine levels in the first 3 years of illness, which decreased thereafter (7). This suggests that heterogeneity in illness duration across studies may explain discrepant results.

Finally, the IOM assessed the possible role of infection in ME/CFS. It found “sufficient evidence suggesting that ME/CFS follows infection with EBV [Epstein-Barr virus] and possibly other specific infections—viral, bacterial and possibly protozoal.” The NIH report called especially for research on herpesviruses.

**Is There a Biological Diagnostic Test?**

As summarized previously, the IOM and NIH reports cited several objective biological abnormalities that help distinguish persons with ME/CFS from healthy control participants and, in some instances, from control participants with other fatiguing diseases, such as depression and multiple sclerosis. However, neither report found conclusive evidence that any particular biomarker was sufficiently sensitive or specific to serve as a diagnostic test.

**Are There Proven Treatments?**

The AHRQ-commissioned review of treatment trials, published in this issue (2), finds that counseling therapies and graded exercise therapy might help improve fatigue and function in some, but not all, patients; that not all trials show a benefit for the average patient; and that neither treatment is curative. Authors of the review warn that exercise therapy must be pursued very cautiously because several trials show that exercise leads to more adverse events and withdrawals. This is not surprising, given that postexertional malaise is a cardinal feature of the illness (1, 5, 8). The review notes that trials of drug treatments typically are of fair or poor quality, that no drug treatments are of proven value, and that some treatments—particularly corticosteroids and galantamine—cause important adverse events.

**What Should Be the Case Definition?**

The IOM committee proposes a new clinical case definition that is simpler than the most widely used re-
search case definition (8). It will likely encompass a more homogeneous and sicker group of persons than the past case definitions and may help discriminate persons with this illness from those with other illnesses associated with fatigue, such as depression (9). However, as Haney and colleagues (4) caution in their AHRQ-commissioned review of diagnostic methods, the proposed new case definition needs thorough testing in many patients with other fatiguing illnesses to ascertain its specificity.

**WHAT SHOULD THE ILLNESS BE NAMED?**

The IOM committee also proposes a new name for ME/CFS: systemic exertion intolerance disease (5). The reason to consider a new name is clear: The name “chronic fatigue syndrome” trivializes this often devastating illness. The U.S. Department of Health and Human Services commissioned the IOM report, and its agencies and advisory bodies will consider the proposed new name and case definition. This includes the Centers for Disease Control and Prevention, which sponsored the IOM’s effort as well as earlier efforts that had resulted in 2 previous case definitions.

These reports from the IOM, AHRQ, and NIH demonstrate how much we have learned about ME/CFS and how much we still do not know. We do not understand its pathogenesis, and we do not have a diagnostic test or a cure. However, these recent reports, summarizing information from more than 9000 articles, should put the question of whether ME/CFS is a “real” illness to rest. When skeptical physicians, many of whom are unaware of this literature, tell patients with ME/CFS that “there is nothing wrong,” they not only commit a diagnostic error: They also compound the patients’ suffering.

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**References**