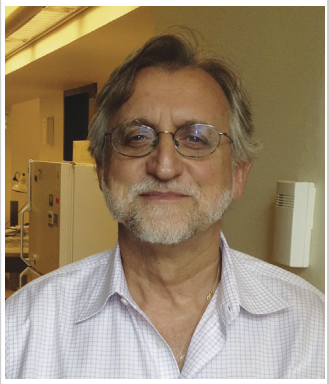
## *Editorial*

# A Timely Multidisciplinary Update on Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome



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Chronic fatigue syndrome (CFS), later named myalgic encephalomyelitis (ME), is characterized primarily by severe, long-lasting fatigue along with dysfunctional homeostasis, especially temperature dysregulation.[1,2] The term *fatigue* was apparently first used in the 1550s in France as *fatiguer* (to tire) from the Latin term *fatigauts*. However, the concept of fatigue (κόπος) was used in 400 BC by Hippocrates and later in 170 AD by Galen.[3] In fact, Galen was the first to write that "severe fatigue will stir up fever," a possible preamble to the dysregulated temperature characterizing ME/CFS.

Scientists have struggled without much success to identify the reason(s) for the severe fatigue in ME/CFS. The obvious presence of subgroups[4] has hampered the identification of objective biomarkers and the development of effective drugs. Studies on viral etiology,[5] mitochondrial or metabolic dysfunction,[6] and fatigue-producing cytokines[7] have been inconclusive when appropriate sedentary controls were included. Recent studies focused on immune dysregulation,[8,9] activation of microglia in the prefrontal cortex of a rat model of fatigue,[10] and localized inflammation in the hypothalamus.[11,12]

In the April and May issues of *Clinical Therapeutics*, a number of experts report on recent findings on the diagnosis, pathogenesis, and treatment of ME/CFS. Two articles in the April issue emphasize current challenges in the recognition and diagnosis of ME/CFS. In his commentary, Natelson[13] discusses the diagnostic criteria for ME/CFS and compares ME/CFS with fibromyalgia syndrome. A case report by Martin–Martinez[14] describes heterogeneity among 3 patients with delayed diagnosis of ME/CFS and highlights the need for clinical physicians to make an early and accurate diagnosis. The subsequent articles in this issue focus on the pathogenesis of ME/CFS. A brief report by Vikse and Omdal[15] describes severe fatigue in patients with mastocytosis, illustrating the contributory role of mast cells and mast cell–derived mediators in the generation of fatigue and sickness behavior. An article by Polli and colleagues[16] examines the association between oxidative stress and the parasympathetic nervous system, whereas an article by Schultz et al[17] discusses the role of autonomic nervous system and orthostatic intolerance. The article by Morris et al[18] reviews a mechanistic model of endocrine-immune regulation and discusses candidate blood biomarkers for ME/CFS, whereas the article by Almenar-Pérez et al[19] presents evidence on epigenetic factors.

Articles devoted to the classification and treatment of ME/CFS will appear in the May issue. A subset of the reported studies will use various *in vitro* and *in vivo* techniques to identify patients with ME/CFS based on the presence of serum autoantibodies or neutralizing antibodies against Epstein–Barr virus deoxyuridine triphosphate nucleotidohydrolase, whereas the remaining articles will present findings on pharmaceutical interventions. Nevertheless, it is obvious from these treatises that we are still far from fully understanding, let alone treating, this complicated and debilitating disorder. Future studies will need to focus on the expression of novel immunoregulatory molecules, especially in the diencephalon, of patients with ME/CFS compared with appropriate controls.

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