Cancer and its treatment commonly result in patient distress, the most frequent aspect of which is fatigue. Fatigue often begins before the cancer is diagnosed, typically increases during the course of cancer treatment, and then declines somewhat but persists at a higher than baseline rate after treatment is completed [1–4]. The most commonly used definition of cancer-related fatigue (CRF) was developed by the National Comprehensive Cancer Network (NCCN) Fatigue Guidelines Committee several years ago [5]. The Committee characterized CRF as “an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning.” CRF differs from the fatigue experienced after muscle exertion, the flu, or overly exuberant celebration, in that it is not relieved by rest and sleep [6,7]. It has both subjective and objective components and may involve dysfunctions in physical symptoms (physical weakness or tiredness), mood (depression), motivation (lack of initiative or motivation), cognition (impairment of cognitive function), and social functions (reduced ability to sustain social relationships) [8].

Fatigue is highly prevalent in patients with cancer and it has a significant impact on patients’ quality of life (QoL) and ability to carry out normal daily activities. Patients report that CRF is more distressing and has a greater impact than other cancer-related symptoms such as pain, depression, and nausea. This impact is magnified by the increasing life expectancy of people with cancer and by the persistence of CRF for months—or even years—after the end of cancer treatment.

In each of the six articles that follow, members of our cancer-control group at the University of Rochester James P. Wilmot Cancer Center provide an in-depth examination of an important dimension of this problem: prevalence, etiology, association with sleep problems, measurement issues, and both pharmacologic and nonpharmacologic management options. The articles are not intended as an exhaustive summary of each area—the field is advancing by the month in some areas—they are instead a snapshot of current knowledge that can serve as a reference point.

The article by Hofman et al. [9] clearly shows the widespread prevalence of CRF and its effects on patients and caregivers. The frequency of fatigue in patients receiving various chemotherapy regimens can range from 70% to 100%, and fatigue is more common in patients with cancer than in the general population and other medical populations [4]. Fatigue has a strong and direct negative impact on all aspects of the QoL of patients with cancer, particularly, their physical well-being. It diminishes their ability to participate in leisure activities [10], to sustain meaningful relationships with their families and others [6], to work, and to engage in social and other activities during and after treatment [11,12]. It also places them in a position of dependence on others for home management, transportation, and even simple self-care activities, such as preparing food and bathing [12–14]. Furthermore, in addition to their inability to participate in a variety of activities, fatigued patients must frequently engage in unwanted behaviors, such as lying down or taking naps, in an attempt to cope with their fatigue [7]. This change in daily activity and self-sufficiency may be demoralizing and discouraging.
Despite the availability of some treatment options and a great deal of ongoing research, fatigue is nevertheless often viewed by clinical staff, caregivers, and the patients themselves as an inevitable consequence of cancer and cancer treatment [15]. This view is unfortunate and is contradicted by the available evidence. In this issue, Mustian et al. [16] provide an overview of the current NCCN recommendations for assessment and management of CRF. Various integrative nonpharmacologic behavioral interventions are available; physical exercise and psychosocial therapy have the strongest scientific evidence supporting their effectiveness. Carroll et al. [17] cite studies that have shown that epoetin alfa and darbepoetin alfa may have value in reducing CRF in patients with anemia. The identification and management of additional comorbidities (i.e., hypothyroidism, malnutrition, emotional distress, etc.) can also be helpful. Most specific treatments for CRF remain experimental, though some agents, such as psychostimulants, including modafinil, have shown promise in open-label prospective trials. New treatment options will likely emerge from several ongoing large-scale clinical trials examining the efficacy of a variety of interventions for CRF, including modafinil, buspirone, American ginseng, L-carnitine, coenzyme Q10, exercise, mindfulness relaxation, and yoga [18].

The article by Jean-Pierre et al. [19] focuses on the measurement of CRF. These authors offer an overview and critique of methods commonly used to assess CRF, as well as a very interesting discussion of the merits of unidimensional versus multidimensional fatigue measures. The primary argument for unidimensional CRF assessment is that, like pain or nausea, patients know when they have it and are quite capable of simply and accurately assessing its presence and severity. Multidimensional CRF measures may be useful in assessing physical, emotional, and cognitive domains. In a related vein, the articles by Roscoe et al. [20], Mustian et al. [16], and Ryan et al. [21] summarize information showing that fatigue may occur as part of a cluster of symptoms including pain, difficulty sleeping, and perceived muscle weakness. The associations among these symptoms might prompt the development of effective integrated treatment strategies.

As pointed out by Roscoe et al. [20], sleep disorders are a common and often chronic problem for both patients with cancer and cancer survivors, and these problems are strongly linked to CRF. Further investigation is warranted in order to better understand the nature of sleep disturbances in patients with cancer and to examine the effectiveness of interventions targeting disordered sleep and daytime sleepiness, both because they are troublesome symptoms in their own right and also as potential treatments for CRF.

The best current thinking on the causes of CRF is outlined in the article by Ryan et al. [21]. They make the case that the etiology of CRF most likely involves the dysregulation of several interrelated physiological, biochemical, and psychological systems. To further complicate matters, the effect of each of these disruptions on CRF not only varies among individuals but also during different phases of the disease and with treatment type. Factors related to the development of CRF covered by Ryan et al. [21] include serotonin dysregulation, hypothalamic–pituitary–adrenocortical axis dysfunction, circadian rhythm disruption, muscle metabolism/ATP dysregulation, and cytokine dysregulation. The authors also examine the contribution of comorbid conditions, such as anemia, cachexia, and depression, to CRF.

These six articles were organized to provide an integrated review of the current understanding and treatment of CRF. It is our hope that their overview of current CRF-related research will prompt new research to allow better understanding and, eventually, better management of cancer-related fatigue.

ACKNOWLEDGMENTS
The author is a recipient of National Cancer Institute grants 1R25-CA102618-01A1 and 2U10CA037420-20, and American Cancer Society grant RSG01071-01-PBP. Publication of this article was supported by a grant from Cephalon, Inc., Frazer, PA.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
G.R.M. has acted as a consultant for MGI Pharma and Cephalon.

REFERENCES
6. Piper BF. Fatigue in cancer patients: Current perspectives on measurement and management. Fifth Annual Conference on Cancer Nursing. In:


