Cancer-related fatigue (CRF) is one of the most common and complex symptoms experienced by patients with cancer, occurring across the spectrum of malignant disease diagnoses and major therapies. Gaining an understanding of the mechanisms underlying this highly prevalent and burdensome symptom is of great interest to researchers and clinicians alike, yet relatively few studies have evaluated the etiology of CRF or the factors that mediate multiple and related physiologic effects (Gutstein, 2001; Wagner & Cella, 2004). The multifactorial and multidimensional nature of CRF has hindered the development of methodologies for evaluating its underlying mechanisms; therefore, the lack of mechanism-driven clinical trials exploring effective pharmacologic therapies has hampered effective CRF management (Lawrence, Kupelnick, Miller, Devine, & Lau, 2004). CRF is a challenging and controversial subject for researchers and clinicians and a significant issue for the many patients with cancer who are unable to get out of bed and function normally. This article will review the clinical correlates of CRF development and propose potential mechanisms underlying the pathophysiology of CRF with support from data related to single and multiple mechanisms.

The pathophysiology of CRF has not been adequately elucidated. Clinical studies have focused on understanding factors that contribute to CRF, including the disease itself, treatments received, and a variety of chronic physical or psychological comorbid conditions, such as anemia, pain, depression, anxiety, cachexia, sleep disturbance, and immobility (see Figure 1). Although several mechanisms for the pathophysiology of CRF have been proposed, little progress has been made toward identifying reliable physiologic markers as objective measures of fatigue.

CRF has been analyzed from physiologic, anatomic, and psychological perspectives (St Clair Gibson et al., 2003). The central governor model posits that fatigue develops in the brain and spinal cord (central fatigue as opposed to peripheral fatigue, which occurs in the neuromuscular junctions and muscle tissues) (Ryan et al., 2007; Weir, Beck, Cramer, & Housh, 2006). Central fatigue, defined as difficulty in the initiation or maintenance of voluntary activities, manifests as a failure to complete physical and mental tasks that require self-motivation and internal cues, in the absence of demonstrable cognitive...
failure or motor weakness (Chaudhuri & Behan, 2004). In this model, to which CRF seems well-fitted, fatigue is a complex emotion affected by motivation and drive, fear and anger, and memory of prior activity. It has been proposed that a centrally mediated disorder of perception may underlie many syndromes with symptoms that lack clear pathophysiologic explanations (St Clair Gibson et al.; Wessely, 2001). Although a failure of nonmotor function of basal ganglia has been proposed as one of the potential pathogenic mechanisms of central fatigue (Chaudhuri & Behan, 2000), little research has been done on human brain imaging of fatigue and whether the conscious sensation of fatigue is associated with particular brain locations or related to whole-brain activity. The inherent subjectivity of CRF has limited the development of preclinical models (Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003).

Establishing the causality of CRF presents numerous difficulties and challenges (Kroenke, 2001). First, not all at-risk patients will experience this symptom. According to National Comprehensive Cancer Network ([NCCN], 2007) guidelines, causes of CRF include the cancer itself, chemotherapy, bone marrow transplantations, immunotherapy and radiation therapy, and anemia; factors identified as frequently contributing to CRF include pain, emotional distress, sleep disturbance, anemia, nutritional deficiencies, cardiac deconditioning, and comorbidities. However, not all patients with these serious conditions will develop fatigue (Mendoza et al., 1999; Mock, 2004). Variability in disease prognosis and response to cancer or symptom treatment (including placebo effects) may further affect symptom development. In addition, CRF is more likely to be caused by multiple risk factors (referred to as a web of causation) than by a single factor. Complex interplay may be seen between the etiologic agent (e.g., cancer treatment, infections, use of central-acting drugs), and host susceptibility. Clinical observations indicate that multiple physical and psychosocial factors are involved for each patient.

**Clinical Correlates of Cancer-Related Fatigue**

**Potential Tumor-Related Causes**

Unusual tiredness often is the first signal that causes people to seek medical care. Significant fatigue often is observed in patients with newly diagnosed cancer, particularly patients with renal or small cell lung cancer who develop paraneoplastic syndrome. Patients with advanced-stage cancer may suffer from more distressing CRF (Brown et al., 2005). Progressive cancer directly affects several organ systems and causes neurophysiologic changes in skeletal muscles. Abnormal production of certain substances (e.g., inflammatory cytokines) may inhibit metabolism or normal muscle function (Kurzrock, 2001; NCCN, 2007). Decreased availability of metabolic substrates in patients with cancer also may be involved (Shaw & Wolfe, 1987). As an example, CRF is one of the main symptoms of cachexia, which presents in about 50% of patients with cancer and is characterized by loss of body mass and skeletal muscle that cannot be explained solely by decreased food intake. Cachexia has been associated with increased levels of certain inflammatory cytokines, including interleukins and tumor necrosis factor-alpha (TNF-α) and may also be related to abnormalities in energy metabolism (Gutstein, 2001; Stasi et al., 2003; Tisdale, 2003).

**Potential Treatment-Related Causes**

**Surgery:** Fatigue, common after major surgery, delays recovery (Rubin, Cleare, & Hotopf, 2004; Rubin, Hardy, & Hotopf, 2004) and usually is attributed to the physiologic response to surgery. Postoperative fatigue has been reported immediately after curative surgery (Forsberg, Bjorvell, & Cedermark, 1996; Galloway & Graydon, 1996; Salmon & Hall, 1997) and may be related to such factors as receipt of anesthesia, type of analgesia, decreased ventilatory capacity, immobilization, infection, or anxiety (Smets, Garssen, Schuster-Uitterhoeve, & de Haes, 1993). The mechanisms of postoperative fatigue have been examined only during early times after surgery. Salman and Hall, in a study of patients who underwent hip arthroplasty, found
that the severity of fatigue after surgery was predicted not by physiologic changes but by the level of fatigue before surgery. In contrast, Rubin, Cleare, et al. suggested that psychological processes are relevant in the etiology of postoperative fatigue. The results from the study relating to mood and expectations suggest that somatization may be important particularly in the first few weeks after surgery, whereas cognitive-behavioral factors and cardiovascular deconditioning may be more important in determining later-stage recovery.

**Chemotherapy:** Nausea, diarrhea, and vomiting induced by chemotherapy can influence CRF symptoms (Gutstein, 2001). CRF also may be associated with anemia or with accumulation of end products from cell destruction (Stasi et al., 2003). Available evidence supports the correlation between anemia and fatigue (Demetri, Kris, Wade, Degos, & Cella, 1998; Turner et al., 2001). Chemotherapy drugs that cross the blood-brain barrier may induce neurotoxicities that produce fatigue (Smets, Garssen, Schuster-Uitterhoeve, & de Haes, 1993). Most patients experience fluctuations in fatigue during high-dose chemotherapy paired with stem cell transplantation, with fatigue increasing as the patients' blood counts approach white blood cell nadir but improving as counts recover (Anderson et al., 2007). The association of fatigue and chemotherapy has been studied extensively in patients with breast cancer (Berger, 1998; Greene, Nail, Fieler, Dudgeon, & Jones, 1994; Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Jacobsen et al., 1999; Pickard-Holley, 1991; Richardson, Ream, & Wilson-Barnett, 1998). Existing anemia and fatigue also can be exacerbated by chemotherapy and radiotherapy (Morrow, Andrews, Hickok, Roscoe, & Matteson, 2002).

**Radiotherapy:** Fatigue may be the most severe symptom experienced by patients during radiation therapy (Wang et al., 2006). Treatment with radiation can lead to anemia, diarrhea, weight loss, anorexia, and chronic pain, any of which can influence fatigue severity (Gutstein, 2001). In a longitudinal study of patients with colorectal cancer receiving chemoradiation, the severity of pain before treatment and the severity of diarrhea during treatment predicted the development of severe fatigue (Wang et al., 2001). Patients who receive radiotherapy may experience a gradual deepening of fatigue with ongoing treatment (Curt, 2000; Wang et al., 2001). Combined modality therapy (e.g., concurrent chemotherapy and radiation) is a known risk factor for persistent fatigue (Jereczek-Fossa, Marsiglia, & Orecchia, 2002).

**Biologic-response modification:** Patients treated with biologic-response modifiers, such as proinflammatory cytokines, may experience such intense and intolerable fatigue that it limits their ability to continue with these agents (Dean et al., 1995; Kirkwood et al., 1985; Robinson & Posner, 1992). Administration of cytokines often results in a flu-like syndrome with a set of symptoms that includes fatigue, fever, chills, headache, myalgias, and malaise (Piper et al., 1989). The most-studied of these biologic agents is interferon-α, which may cause fatigue in about 70% of patients and may induce hypothyroidism, which also may cause fatigue in up to 20% of patients (Kirkwood et al., 2002).

**Hormone therapy:** Side effects of hormone therapy have not been well assessed and are frequently underestimated (Obe, 1996). Lethargy and lack of energy related to hormone treatment have been reported in patients with breast cancer (Leonard, Lee, & Harrison, 1996). Hormone ablation may double the incidence of reported fatigue in patients with prostate cancer, which supports the correlation between gonadotrophin function and fatigue (Stone, Hardy, Huddart, A'Hern, & Richards, 2000).

**Cancer-Related Fatigue in Cancer Survivors**

Patients have repeatedly identified CRF as the most distressing symptom during the acute phase of cancer treatment, and literature shows that CRF may continue for years after treatment is completed, even after the cancer is cured. Cancer survivors' functioning may be affected to such an extent from CRF that they can no longer complete routine tasks at work or in the home setting (Bower et al., 2000, 2005; Servaes, Verhagen, & Bleijenberg, 2002).

**Relationship of Fatigue to Other Symptoms**

Although fatigue often is singled out as the most common symptom across many different diseases, it almost always clusters with other significant symptoms. The greater the number of symptoms and perceived disabilities, the more likely clinicians are to identify psychological, behavioral, or social contributors to illness (Wessely, 2001). Cluster analyses of multiple cancer symptoms, such as fatigue, pain, and sleep disturbance, have confirmed this phenomenon (Cleeland, 2007; Dodd, Miaskowski, & Paul, 2001) and are consistent with observations from patients with cancer who rarely have solitary symptoms during active therapy or with advanced disease and who often experience accompanying medical comorbidities and psychological disorders (Hickok, Morrow, Roscoe, Mustian, & Okunieff, 2005; Hoffman, Given, von Eye, Gift, & Given, 2007).

**Pain and sleep disturbance:** The interaction of fatigue with pain and sleep disturbance has been well addressed in the symptom literature (Berger & Farr, 1999; Berger, Farr, Kuhn, Fischer, & Agrawal, 2007; Bower et al., 2000; Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999; Lee, 2001; Mock et al., 2001; Schwartz, Mori, Gao, Nail, & King, 2001). Parameter estimates in patients newly diagnosed with lung cancer indicated that the three-way interaction of pain, fatigue, and insomnia was statistically significant (Hoffman et al., 2007). Higher total and subscale fatigue scores were correlated with most components of poorer subjective sleep quality (r = 0.25–0.42, p ≤ 0.005) (Berger et al.).

**Distress and depression:** Chronic emotional distress can contribute to CRF development (Irvin et al., 1994; Jacobsen et al., 1999). Proposed mechanisms include dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis (Scott & Dinan, 1999). In an international study by Skapinakis, Lewis, and Mavreas (2004) of chronic fatigue syndrome in the primary care setting, a temporal relationship between fatigue and depression, when adjusted for demographics, physical morbidity, and intercenter variability, supported the concept that unexplained fatigue and depression might act as independent risk factors for each other. Also hypothesized is that the activation of inflammatory pathways in otherwise healthy individuals may influence individual depression-related symptoms, such as fatigue, insomnia, and anger or hostility (Raison, Capuron, & Miller, 2006; Suarez, Lewis, Krishnan, & Young, 2004).

**Other pathophysiologic conditions:** Physical conditions, such as various infections, malnutrition, thyroid dysfunction,
and other organ failure could either cause or contribute to CRF. Multiple physical symptoms interact with affective symptoms, and the patient’s perception of illness, coping skills, and mood may have important and long-lasting effects on eventual adaptation to chronic fatigue and should be considered for effective intervention. Edwards, Suresh, Lynch, Clarkson, and Stanley (2001) studied illness representations by patients with chronic fatigue, and their work should be used as a basis for further research.

Proposed Mechanisms of Cancer-Related Fatigue Pathophysiology

Although the underlying etiology of and risk factors for CRF are not fully resolved, the following hypotheses provide independent and overlapping potential mechanisms for the pathophysiology of this complex phenomenon. These proposed mechanisms include proinflammatory cytokines, growth factors, circadian rhythm modulation, HPA axis disruption, serotonin dysregulation, vagal-afferent activation, anemia, and abnormalities of generation or use of adenosine triphosphate (Cleeland & Wang, 1999; Kurzrock, 2001; Lee et al., 2004; Morrow, Andrews, et al., 2002; Ryan et al., 2007).

Proinflammatory Cytokine Hypothesis

Symptoms reported by patients with cancer undergoing treatment are strikingly similar to characteristics of the evolving animal models of cytokine-induced sickness behavior (Cleeland et al., 2003; Lee et al., 2004; Miller, 2003). Sickness behavior refers to clusters of behavioral and physiologic responses (e.g., hyperalgesia, sleep disturbance, reduced activity, reduced food intake) observed in animals after physical insult or administration of inflammatory agents or specific proinflammatory cytokines (Dantzler, 2001; Hart, 1988; Kent, Bluthe, Kelley, & Dantzer, 1992). Growing awareness suggests that cytokines play a mechanistic role in CRF as common biologic mechanisms (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006; Dodd et al., 2005; Dunlop & Campbell, 2000; Skapinakis et al., 2004; Wang et al., 2006). The theoretical underpinning for the proinflammatory cytokine hypothesis, based on the animal model of inflammation-induced sickness behavior, is that dysregulated inflammation and its downstream toxic effects represent a significant biologic basis for subjectively reported CRF and a cluster of other symptoms (Cleeland et al.; Lee et al.; Payne, 2006).

Cytokine dysregulation appears to play a part in cancer-related symptom production. Elevated inflammatory biomarkers (e.g., interleukin-6 [IL-6], TNF-α) have been shown in studies of persistent fatigue in survivors of breast cancer (Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006) and may be associated with a chronic inflammatory process involving the T-cell compartment (Bower, Ganz, Aziz, Fahey, & Cole, 2003). In patients with advanced cancer, cachexia-related tissue catabolism is reported to be mediated by IL-6 and TNF-α (Argiles, Busquets, & Lopez-Soriano, 2006).

Increased inflammation also is a prime candidate for the mechanism behind increases in treatment-related symptoms. The insult of cancer treatment, including radiotherapy and chemotherapy, increases production of inflammatory cytokines, particularly IL-6 and TNF variants (Linard et al., 2004, 2005). Increases in IL-6 in response to paclitaxel therapy for patients with breast cancer have been associated with reported symptoms (Pusztai et al., 2004). Patients with CRF exhibit elevations in IL-6, IL-1 receptor antagonist, IL-1, and TNF, along with decreased albumin (Meyers, Albitar, & Estey, 2005).

Researchers have suggested that reduction of this treatment-induced inflammatory response might significantly reduce the morbidity associated with radiotherapy (Garden, 2003). The use of the TNF inhibitor etanercept was associated with significantly less fatigue in patients with cancer, along with a trend for lower mean nuclear factor-kappa B (a cytokine precursor molecule) activity (Madhusudan et al., 2005). Prechemotherapy and chemotherapy-induced changes in inflammation have been related to changes in fatigue and quality of life (Mills, Parker, Dimsdale, Sadler, & Ancoli-Israel, 2005).

Molecules downregulated by cytokines, such as albumin and C-reactive protein, also show a high correlation with CRF presence. For example, fatigue was associated with low albumin in patients with hematologic malignancies and with greater C-reactive protein in patients with advanced lung cancer (Brown, McMillan, & Milroy, 2005; Wang et al., 2002).

Schubert, Hong, Natarajan, Mills, and Dimsdale (2007) reviewed 18 well-designed studies (N = 1,037) to evaluate the strength of evidence supporting the relationship between inflammation and fatigue. Analyses based on weighting according to sample size showed a significant positive correlation between fatigue and levels of circulating inflammatory markers (r = 0.11, p < 0.0001). Analyses of individual inflammatory markers revealed significantly positive correlations between fatigue and IL-6 (r = 0.12, p = 0.004), IL-1 receptor antagonist (r = 0.24, p = 0.0005), and neopterin (r = 0.22, p = 0.0001). A possible reason for the insignificant correlation with IL-1β or TNF-α was because serum TNF-α was not detectable, possibly from the sampling process, storage conditions, or duration (Schubert et al.; Thavasu, Longhurst, Joel, Slevin, & Balkwill, 1992).

Growth Factor Hypothesis

The growth factor hypothesis posits that vascular endothelial growth factor (VEGF) level is associated with treatment-induced fatigue. VEGF is an angiogenic cytokine with high relevance to cancer, stimulating the formation of new blood vessels necessary for tumor growth and metastasis (Boudreau & Myers, 2002) and an independent predictor of poorer survival (Nishimura et al., 2000). Patients with breast cancer undergoing chemotherapy were found to have significantly increased fatigue and reduced quality of life correlated with elevated VEGF and soluble intracellular adhesion molecule-1 levels (Mills et al., 2005). Sunitinib is a VEGF receptor inhibitor that is hypothesized to decrease thyroid function by preventing binding of VEGF to normal thyroid cells or impairing thyroid blood flow, which results in thyroiditis. Sunitinib-induced hypothyroidism (without autoantibodies) has been observed in patients with advanced renal cell cancer (Rini et al., 2007) or gastrointestinal stromal cancer (Desai et al., 2006). Thyroid hormone replacement improved fatigue and other symptoms in 9 (53%) of 17 patients with renal cancer (Rini et al.).
Circadian Rhythm Modulation Hypothesis

Research examining possible links between circadian rhythms and CRF has focused on secretion rhythms of the stress hormone cortisol and on rest/activity patterns. Preclinical studies have shown that epidermal growth factor receptor (EGFR) ligands, such as transforming growth factor-alpha (TGF-α), inhibit hypothalamic signaling of rhythmic behavior. Clinical observations indicate that elevated levels of TGF-α are associated with fatigue, flattened circadian rhythms, and loss of appetite in patients with metastatic colorectal cancer (Rich et al., 2005). A slower decline in salivary cortisol levels correlated with increased fatigue severity was observed in fatigued cancer survivors over the course of the day (Desai et al., 2006). The data support the hypothesis that a symptom cluster of fatigue, appetite loss, and sleep disruption commonly seen in patients with cancer may be related to EGFR ligands, released either by the cancer itself or by the host in response to the stress associated with cancer, and suggest that further examination of their role in the production of symptom clustering is warranted (Rich, 2007).

Sleep disorders are commonly observed in patients with cancer and may result from altered circadian rest/activity rhythms. An inverse correlation between fatigue and daily activity levels and a positive correlation between fatigue and restless sleep at night have been reported (Berger, 1998; Mormont et al., 1998). Changes in fatigue between chemotherapy cycles also have been correlated with changes in the rest/activity rhythm (Roscoe et al., 2002). The association between fatigue and circadian disruption was reported as being independent of the presence of depression, although depression did correlate with altered circadian rhythm.

Serotonin Dysregulation Hypothesis

The theory behind dysregulation of serotonin as an explanation of CRF is that cancer and its treatment cause an increase in brain serotonin (5-hydroxytryptamine [5-HT]) levels in localized regions of the brain and an upregulation of certain 5-HT receptors. This can lead to decreases in somatomotor drive, modified HPA axis function, and a sensation of decreased capacity to perform physical work (Andrews Morrow, Hickok, Roscoe, & Stone, 2004; Gandevia, Allen, & McKenzie, 1995; Newsholme & Blomstrand, 1995). Taken primarily from studies of exercise-induced fatigue or chronic fatigue syndrome, increased evidence supports a role for 5-HT metabolism and neurotransmission in the genesis of central fatigue. Animal studies have shown that 5-HT concentrations increase in the hypothalamus and brain stem with sustained exercise, reaching a maximum at the point of fatigue (Bailey, Davis, & Ahlborn, 1993; Blomstrand, Perrett, Parry-Billings, & Newsholme, 1989). Similarly, administration of 5-HT to rats produced a dose-related decrease in running endurance (Bailey, Davis, & Ahlborn, 1992), whereas administration of a 5-HT antagonist improved performance (Bailey et al., 1993). Studies in patients with chronic fatigue syndrome have demonstrated increased plasma levels of free tryptophan, which could potentially lead to high levels of central 5-HT (Badawy, Morgan, Llewelyn, Albuquerque, & Farmer, 2005; Castell, Yamamoto, Phoenix, & Newsholme, 1999). In several human studies, administration of selective serotonin reuptake inhibitors has been shown to reduce the capacity to perform exercise. However, other investigators have shown that central 5-HT concentrations do not influence CRF (Morrow et al., 2003; Roscoe et al., 2005).

Hypothalamic-Pituitary-Adrenal Axis Disruption Hypothesis

The HPA axis is the central system regulating release of the stress hormone cortisol. The HPA disruption hypothesis proposes that cancer or its treatment either directly or indirectly causes alterations in HPA function, leading to endocrine changes that either cause or contribute to fatigue (Behak, Behan, Dinan, Gray, & O’Keane, 1992; Bower et al., 2005; Swain & Maric, 1995). Fatigue has been associated with reduced HPA axis function, such as defective central corticotropin-releasing hormone release and downregulation of corticotropin-releasing hormone receptors in response to chronic stress, and with hypo-cortisolemia in patients with cancer, chronic fatigue syndrome, and rheumatoid arthritis (Ryan et al., 2007). Alterations in HPA axis function may be caused by various factors in patients with cancer. For example, proinflammatory cytokines (e.g., IL-1, IL-6, TNF-α) and some comorbidities (e.g., sleep disturbance) can stimulate the HPA axis (Vgontzas & Chrousos, 2002; Wichers & Maes, 2002). Certain cancer treatments (e.g., glucocorticoids, radiotherapy, some chemotherapeutic regimens) may lead to direct suppression of the HPA axis (Del Priore, Gurski, Warshal, Angel, & Dubeshiter, 1995; Morrow, Hickok, Andrews, & Stern, 2002; Schmiegelow et al., 2003). Cortisol has an inhibitory effect on cytokine production; therefore, cytokine levels may rise in the presence of reduced cortisol concentrations (Petrovsky, McNair, & Harrison, 1998).

Vagal-Afferent–Activation Hypothesis

Based on animal studies, the vagal-afferent-activation hypothesis suggests that cancer and its treatment cause peripheral release of a spectrum of neuroactive molecules (e.g., serotonin, cytokines, prostaglandins) that may activate vagal-afferent nerves (Blackshaw & Grundy, 1993; Ek, Kurosawa, Lundeberg, & Ericsson, 1998; Niijima, 1996). The overall effects may manifest as decreased somatic motor output and sustained changes in particular regions of the brain associated with fatigue by induction of IL-1β sickness behavior (Hansen & Krueger, 1997; Opp & Toth, 1998). In response to injection of IL-1β, the vagal-afferent nerves of rats mediate IL-1β production at multiple sites in the central nervous system (Hansen, Taishi, Chen, & Krueger, 1998). Considering the effect of the HPA axis on fatigue, cytokine production in the hypothalamus is particularly significant.

Anemia Hypothesis

Cancer-related anemia has a profound impact on patients experiencing the associated complications of fatigue, dyspnea, palpitations, dizziness, and decreased cognitive function (Cella,
Gaining an understanding of the specific mechanisms related to fatigue development in patients with cancer and survivors requires further investigation. Pathophysiologic research of CRF could be applied in the clinic to improve CRF diagnosis and administration of mechanism-driven interventions.

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