Cancer-related fatigue (CRF) is influenced and modulated by a number of critical factors, and the mechanism that is both necessary and sufficient to induce development of severe fatigue in patients with cancer has not yet been identified. Specific research efforts to understand the factors that may contribute to CRF development have been made, including studies of the direct effects of tumor burden, the effects of cancer treatment, and other pathophysiologic and psychosocial conditions. Compelling new hypotheses regarding CRF pathophysiology have been proposed, such as the pro-inflammatory hypothesis, the serotonin hypothesis, the vagal-afferent–activation hypothesis, the anemia hypothesis, and the adenosine triphosphate hypothesis; some of these have been tested in both animal models and humans and some in animals only. Gaining an understanding of the specific mechanisms related to the development of fatigue in patients with cancer and survivors requires further investigation. Pathophysiologic research in CRF could be applied in the clinic to improve CRF diagnosis and to enable administration of mechanism-driven interventions. A targeted intervention study with CRF as a primary end point also would be useful.

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

At a Glance

- The pathophysiology of cancer-related fatigue (CRF) has not been adequately elucidated to date.
- No physiologic markers of CRF have been established from ongoing research with hypotheses proposing underlying mechanisms.
- A web of causation may be reflected in an interaction of etiology and host susceptibility.

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