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.