

# Are the Symptoms of Cancer and Cancer Treatment due to a Shared Biologic Mechanism?

## *A Cytokine-Immunologic Model of Cancer Symptoms*

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**BACKGROUND.** Cancers and cancer treatments produce multiple symptoms that collectively cause a symptom burden for patients. These symptoms include pain, wasting, fatigue, cognitive impairment, anxiety, and depression, many of which co-occur. There is growing recognition that at least some of these symptoms may share common biologic mechanisms.

**METHODS.** In November 2001, basic and clinical scientists met to consider evidence for a cytokine-immunologic model of symptom expression along with directions for future research.

**RESULTS.** The characteristics of cytokine-induced sickness behavior in animal models have much in common with those of symptomatic cancer patients. Sickness behavior refers to a set of physiologic and behavioral responses observed in animals after the administration of infectious or inflammatory agents or certain proinflammatory cytokines. In some cases, these responses can be prevented by cytokine antagonists. A combination of animal and human research suggests that several cancer-related symptoms may involve the actions of proinflammatory cytokines.

**CONCLUSIONS.** Based on the similarities between cancer symptoms and sickness behavior, the authors discussed approaches to further test the implications of the relationship between inflammatory cytokines and symptoms for both symptom treatment and symptom prevention. *Cancer* 2003;97:2919–25.

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Cancer patients may suffer from numerous symptoms resulting from the primary disease and/or from the treatment of disease. Collectively, these sources of distress impose a symptom burden on the patient that is the subjective counterpart of the tumor burden caused by the disease.<sup>1</sup> These symptoms are categorized under terminologies such as pain, gastrointestinal symptoms (e.g., nausea, diarrhea), wasting/cachexia, fatigue, cognitive impairments, anxiety, and depression. Symptoms can cause treatment delays or lead to premature treatment termination, may impair function and rehabilitation, and cause significant distress.<sup>2,3</sup>

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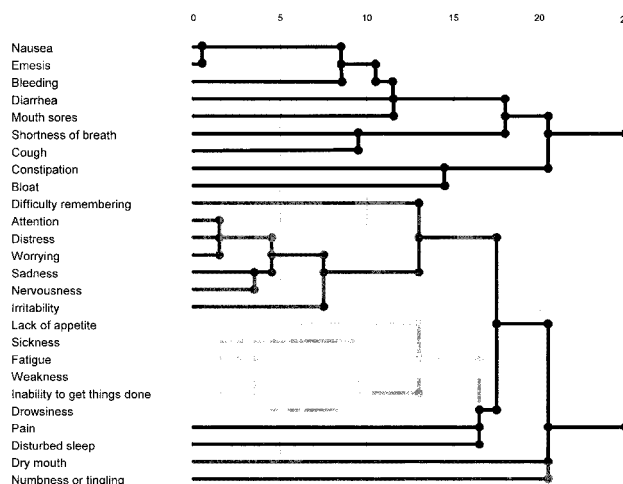
There is growing awareness that common biologic mechanisms may underlie or contribute to at least some of those symptoms simultaneously.<sup>3,4</sup> This is exemplified in the animal models of sickness behavior, which have symptoms in common with those of cancer patients. Sickness behavior refers to a constellation of physiologic and behavioral responses observed in animals after the administration of inflammatory agents or specific proinflammatory cytokines.<sup>5-9</sup> Because of the apparent connection between symptoms and biologic mechanisms, careful description of cancer-related symptoms and correlation of these symptoms with clinical laboratory data, coupled with preclinical research studies, is an important area for future programmatic research. A working group on cytokines and cancer-related symptoms met in November 2001 to discuss a unifying biologic/physiologic framework that could provide direction and coordination for future descriptive, laboratory, and clinical research pertaining to understanding cancer-related symptoms and identifying new symptom treatment strategies.

### Current Status of Clinical Symptom Description

The symptoms of cancers and their treatments have been studied in some detail. Numerous clinical tools, including numeric rating scales, visual analog scales, and verbal descriptive scales, have been used to assess and measure symptoms. Most symptoms are identified and their severity judged by the subjective reports of the patient, although some symptoms (such as cognitive impairment) must be identified by performance measures. Observational data often amplify and supplement subjective reports. The measurement of symptoms and the development of symptom assessment tools have matured to the point where credible descriptive and epidemiologic clinical studies of symptoms can be performed.

In an overall sense, however, the clinical studies of cancer symptoms have a number of shortcomings. Symptoms, as described and "labeled," often are assessed and treated as separate and mutually exclusive entities (for instance, pain, fatigue, and depression). Often, symptoms are evaluated and reported without stratifying for heterogeneity with respect to disease type, disease treatment, and response to disease treatment. Durations of symptoms may be days, months, or years, but assessments often are performed cross-sectionally rather than longitudinally.

When symptoms are grouped, the grouping often is done intuitively rather than empirically. Physical symptoms (pain, nausea, diarrhea, fatigue, wasting/cachexia) commonly are dissociated from cognitive symptoms (poor problem solving, memory, attention) and affective symptoms (anxiety and depression). However, based on observed associations, plausible relationships among



**FIGURE 1.** Relative distance among symptoms associated with cancer and cancer treatment.<sup>2</sup> This diagram shows the results of a cluster analysis of the responses of 527 outpatients undergoing cancer therapy, as well as the symptoms that occur either together or independently. We used hierarchical cluster analysis to identify clustering of symptom items. Clusters were formed using the average linkage (centroid method) between symptom items and the distances between symptom items were calculated using squared Euclidian distances. This visual representation shows the symptom items that are related (connected vertical lines) and the distances between symptom items at each step in the analysis. The distance values of 0 to 25 represent relative distances. Reading from left to right, the data show a tight relationship between clusters of cognitive and affective symptoms. Symptoms that cluster earlier in the analysis (toward the left side) are identified by patients as occurring together. For example, the fatigue-related symptom cluster is associated more closely with affective disturbances and cognitive impairment than with the gastrointestinal and respiratory symptom clusters. Conversely, pain and sleep disturbances remain separate from other symptoms for several steps in the analysis, indicating that they are identified independently. The same is true for dry mouth and numbness. *Cancer*. 2000;89:1634-1646. ©2000 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

these symptoms are more complicated. Figure 1 diagrams the relative distances and relations between major symptoms reported by patients receiving cancer treatment.<sup>2</sup> This analysis demonstrates a tight correlation between clusters of cognitive and affective symptoms. Other clusters include gastrointestinal symptoms, respiratory symptoms, and fatigue-related symptoms. The fatigue-related symptom cluster is associated more closely with affective disturbances and cognitive impairment than with gastrointestinal and respiratory symptoms. Pain and sleep disturbance are identified relatively independently of other symptoms.

The analysis in Figure 1 is presented as preliminary and illustrative, rather than definitive. It is not stratified for the type of cancer or the type of treatment. However, the clustering of symptoms raises the possibility that a given cluster may share underlying biologic mechanisms that differ from those of other clusters.

Associations between symptoms may also be apparent on the basis of temporal (longitudinal) analyses and on the basis of responses to treatment for the cancer or to treatment for the symptoms. For example, in a study of melanoma patients treated with interferon- $\alpha$  (IFN- $\alpha$ ) as immunotherapy,<sup>10</sup> symptoms were assessed over a 12-week period. Pain, gastrointestinal symptoms, wasting, and fatigue began earlier (within 2 weeks), whereas cognitive impairment and depression began later. Because of the symptoms anticipated with IFN- $\alpha$  treatment (particularly depression), patients were randomized to receive paroxetine (a selective serotonin reuptake inhibitor-type antidepressant) or placebo, starting 2 weeks before IFN- $\alpha$ . All symptoms were ameliorated by paroxetine, but the amelioration was more evident for pain, cognitive impairment, and depression than for gastrointestinal symptoms, wasting, and fatigue.

As another example of the complexities of symptom assessment, cognitive function studies performed on untreated cancer patients suggest the subclustering of impairments as follows: memory, motor dexterity, and executive functions (frontal subcortical components) were impaired concurrently, whereas attention and psychomotor speed were not;<sup>11</sup> working memory (ability to process information and do multiple tasks) often was impaired, whereas hippocampal components of memory (retention and consolidation) were not.<sup>12</sup>

Descriptive studies of the symptoms of cancer patients are far from comprehensive, but are consistent with the hypothesis that symptoms may have natural associations with each other that reflect the underlying mechanisms. There is a need to explore symptom associations more systematically and to design and coordinate clinical studies so as to better understand possible common mechanisms for symptoms that form clusters.

### Preclinical Evidence Consistent with Roles for Cytokines in Symptom Production

Sickness behavior can be elicited in animal models by bacterial infections and by administration of pathologic components of bacteria such as lipopolysaccharides (LPS). Physiologic components of sickness behavior include acute-phase responses (fever, systemic depletion of minerals), pain (hyperalgesia), wasting, and increased activity of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system.<sup>6</sup> Behavioral components include a general decrease in activity, somnolence, cognitive impairment (impaired learning), decreased social interaction and exploration, decreased sexual activity, and decreased eating.<sup>13</sup> Sickness behavior in animals includes many similarities to some of these cancer-related symptoms.

Sickness behavior requires immune-to-brain

communication that orchestrates this array of responses.<sup>6,8,9</sup> The binding of LPS to macrophages initiates a cascade of proinflammatory cytokine release and activates other immune cells, including lymphocytes and neutrophils. The responses characteristic of sickness behavior can be elicited by systemic administration of proinflammatory cytokines including interleukin (IL)-1, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IFN- $\alpha$ , and IL-2, administered subcutaneously, intravenously, or intraperitoneally.<sup>5-9,14-21</sup> In some cases, cytokine antagonists can prevent some components of sickness behavior. For example, the LPS-induced inflammatory cascade leading to pain and other symptoms can be attenuated by antagonists of the IL-1 and TNF- $\alpha$  receptors.<sup>8,9,15,20-22</sup> Peripheral cytokines may elicit symptoms by multiple pathways.<sup>6,8,9,23,24</sup> The rapid pathway involves cytokine actions at primary afferent neurons of peripheral nerves, such as the vagus, that innervate sites of infection and immune responses, including the abdominal cavity. The cytokine actions may include directly producing discharge of nerve fibers.<sup>25-27</sup> The slow pathway starts with cytokine production by macrophages that can act on the circumventricular organs (CVOs) and choroid plexus surrounding brain ventricles. These regions have no blood-brain barrier. Interleukin-1, which enters or is produced in CVOs, may act via IL-1 receptors in the area postrema, the median eminence, and the organum vasculosum laminae terminalis, to trigger signaling cascades.

Proinflammatory cytokines play a central role in preclinical models that focus more specifically on the symptom of peripheral neuropathic pain/hyperalgesia (hypersensitivity to cutaneous stimuli). In the rat chronic constriction injury (CCI) model, structural damage to peripheral axons leads to an inflammatory reaction at the site of injury and to neuropathic pain.<sup>28-30</sup> In another rat model (peripheral neuritis), the sciatic nerve is exposed at the mid-thigh level and coated with an immune stimulant such as carrageenan or complete Freund's adjuvant.<sup>31</sup> Inflammatory cells (macrophages, neutrophils, and CD4<sup>+</sup> and CD8<sup>+</sup> T cells) infiltrate the site, levels of inflammatory cytokines (IL-1, leukemia inhibitory factor, and particularly TNF- $\alpha$ ) increase, and endoneurial swelling and neuropathic pain ensue. The inflammatory cascade leading to pain can be blocked by thalidomide (presumed to block TNF- $\alpha$ ) in the case of the CCI model and by thalidomide or cyclosporin A (an immunosuppressant drug) in the case of the neuritis model.<sup>29,30,32,33</sup>

Experimental animals, like humans, develop peripheral neuropathic pain following treatment with the chemotherapeutic agents vinca alkaloids, taxanes, and cisplatin.<sup>34-37</sup> In both humans<sup>38</sup> and animals,<sup>39</sup> exposure to gamma irradiation also often produces

neuropathic pain-like syndromes and insensitivity to the analgesic properties of morphine. Peripheral neuropathy could be due, at least in part, to the induction of proinflammatory cytokines around nerve endings. For example, production by immune cells and/or cancer cells of the proinflammatory cytokines IL-1, IFN- $\alpha$ , and TNF- $\alpha$  can be increased by exposure to paclitaxel,<sup>40,41</sup> cisplatin,<sup>42,43</sup> or irradiation.<sup>44,45</sup>

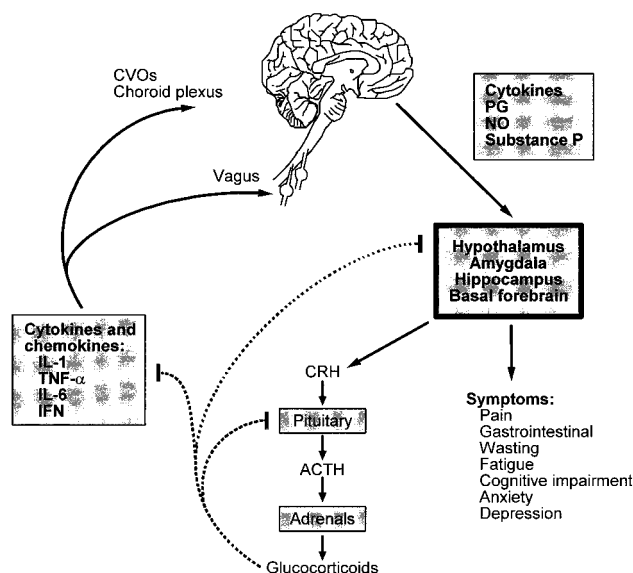
### Clinical Evidence Consistent with Roles for Cytokines in Symptom Production

The hypothesis that cytokines may play a mechanistic role in cancer-related symptoms is consistent with various clinical observations. Noncancer patients who received cytokine therapy displayed many of the symptoms that are observed in cancer patients. For example, patients with hepatitis C virus infection and those with the acquired immunodeficiency syndrome (AIDS) who received IFN- $\alpha$  therapy endured symptoms of pain, fatigue, cognitive impairment, psychosis, and depression.<sup>46–48</sup> A similar symptom profile was observed among patients with renal cell carcinoma, chronic myelogenous leukemia, melanoma, all of whom received IFN- $\alpha$ , IL-2, or IFN- $\alpha$  plus IL-2.<sup>10,49–54</sup> Concurrent administration of oral dexamethasone (an immunosuppressant) and high-dose IFN- $\alpha$  significantly reduced the occurrence of influenza-like symptoms and fatigue in patients with advanced renal cell carcinoma.<sup>49</sup> Interleukin-6 induced fatigue, inactivity, and poor concentration when administered to normal subjects.<sup>55</sup>

Neuropathic pain is a frequent complication of chemotherapy with vinca alkaloids, taxanes, and cisplatin and often persists long after treatment has ended.<sup>56</sup> Psychophysical studies of chemotherapy-induced neuropathic pain demonstrated multiple zones of sensory disturbance<sup>57,58</sup> similar to those observed in cancer and noncancer patients experiencing pain after cytokine therapy.<sup>46,47</sup>

Preliminary clinical studies of patients with myelodysplastic syndrome and acute leukemia before treatment revealed correlations between the more severe symptoms (fatigue, cognitive impairment, and reduced quality of life) and increased levels of cytokines (IL-1 receptor antagonist, TNF- $\alpha$ , IL-6, IL-8, and epidermal growth factor).<sup>12</sup> Other preliminary evidence suggested that fatigue is associated with elevations in such proinflammatory cytokines as IL-1, IL-6, TNF- $\alpha$ , and IFNs.<sup>54</sup>

Cell types that are potential sources of cytokines and other immunoregulatory factors in cancer patients include the cancer cells themselves,<sup>41</sup> immune cells (neutrophils, macrophages, lymphocytes),<sup>8,9,40,42–45</sup> and nervous system cells (paraganglial cells, glial cells



**FIGURE 2.** Biologic/physiologic mechanistic framework for cytokine-induced sickness behavior.<sup>9</sup> In the afferent arm (solid lines), proinflammatory cytokines and chemokines (interleukin [IL]-1, tumor necrosis factor [TNF]- $\alpha$ , IL-6, interferon [IFN]- $\alpha$ , and IFN- $\gamma$ ) are released in the periphery by activated immune cells. They exert their effects on peripheral nerves and directly on the brain to induce various aspects of the sickness response. These behavioral/physiologic changes are elicited by mediators acting downstream from the cytokines. Glutamate, nitric oxide, prostaglandins, and substance P act on brain regions, including the paraventricular nucleus of the hypothalamus and the amygdala.<sup>6,8</sup> Turnover of monoamines (serotonin, dopamine, norepinephrine) in these brain regions is affected.<sup>19,61–63</sup> Availability of monoamine precursors (e.g., tryptophan) may be decreased.<sup>9,64,65</sup> The hypothalamic-pituitary-adrenal axis is activated,<sup>15,19,61,62,66,67</sup> with up-regulation of the plasma concentrations of corticosteroids, which in turn can provide feedback (dotted lines) to limit cytokine production.<sup>68</sup> Other mediators, such as the antiinflammatory cytokine IL-10,<sup>54,64</sup> also have roles in activation and regulation of responses. ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing hormone; CVO: circumventricular organ; NO: nitric oxide; PG: prostaglandin.

[astrocytes, oligodendrocytes, microglia], and Schwann cells).<sup>6,8,59,60</sup>

### Working Group Conclusions and Future Directions

Animal models and clinical evidence suggest that many of the symptoms experienced by cancer patients may be mediated by cytokines acting on the peripheral and central nervous systems. Figure 2 shows a biologic/physiologic mechanistic framework for cytokine-induced sickness behavior and cancer symptoms. Many of the components of this framework are relatively unsubstantiated (e.g., suggested by correlation only). Consequently, strategies that combine basic science and clinical research approaches are needed. If aggressively and systematically pursued, these strategies could lead to substantiation and/or

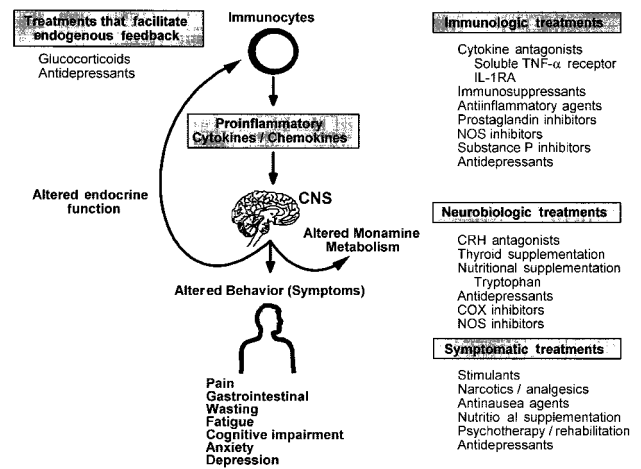
modification of the framework and could yield new approaches to symptom treatment.

Clinical research would begin with large-scale descriptive studies with symptomatic cancer patients. Studies would assess simultaneously several symptoms that are most distressing to patients (pain, wasting/cachexia, fatigue, cognitive impairment, and depression). Assessments should be repeated over time so that changes in symptom severity and patterns related to disease status, treatment status, and intercurrent system disorders can be identified. Data regarding potential biologic markers of symptom mechanism should be collected simultaneously. Such biologic markers could include circulating concentrations of cytokines, acute-phase proteins, hormones of the HPA axis, and tryptophan.

Cognitive and affective assessments, symptom reporting tools, and measures of potentially correlated biologic variables should be standardized across study sites to enable the establishment of a large database that might yield common patterns. Multivariate descriptive analysis would help to identify patterns of co-occurring symptoms and correlations with biologic markers that may suggest common biologic mechanisms. Novel covariates, such as gene expression profiling by microarray analyses, might be able to identify relevant molecules. Biologic/mechanistic analyses can be extended to the cellular level to investigate the role(s) of particular cell types responsible for the production of mediators. Involved immune cells can also be studied in vitro and the relevant factors (e.g., tumor antigens, cytokines) that might affect their involvement can be examined directly.

Clinical studies may be undertaken to evaluate therapeutic interventions for ameliorating symptoms and to probe simultaneously mechanistic pathways. Such clinical studies could address systematically the various steps involved in the translation of cytokine signals to alterations in behavior. As noted in Figure 3, there are several potential targets for intervention. Novel interventions that target cytokines and other potential mediators (especially interventions for which the mechanisms of action are understood and can be monitored. A review of potential treatment strategies (Fig. 3) will help to refine and test the framework presented in Figure 2, especially if applied along with behavioral and biologic/mechanistic assessments in a broad-based, coordinated fashion.

It may become possible to apply new and existing medications to immunologic and neurobiologic targets, rather than to specific symptoms. Therapeutic interventions that target cytokines and their receptors are highly promising candidates for suppressing and perhaps even protecting against the development of cancer-related symptoms. Challenges to developing



**FIGURE 3.** Treatment strategies for cancer-related symptoms. The center flow diagram is a modification of the sickness response illustrated in more detail in Figure 2. Sites for the implementation of treatments directed at the sickness response circuit are shown. (1) Immunologic treatments (such as soluble receptors of TNF- $\alpha$  and IL-1 receptor antagonists) that are designed to inhibit cytokine signaling directly, or treatments that block downstream mediators of inflammation, including prostaglandins, nitric oxide, and substance P; (2) neurobiologic treatments that target central nervous system (CNS) mediators of behavioral alterations including the monoamines and corticotropin-releasing hormone (CRH); (3) symptomatic treatments (such as narcotics for alleviation of pain, stimulants to combat fatigue, antidepressants for relief from depression) that address the ultimate manifestations of upstream mediators; and (4) treatments designed to take advantage of the normal endogenous feedback circuits that limit sickness responses in settings such as viral illness. CNS: central nervous system; CRH: corticotropin-releasing hormone; COX: cyclooxygenase; NOS: nitric oxide synthase. Figure after A. H. Miller.

such therapies will include ensuring that the therapies do not exacerbate the cancer by weakening the patients' immunologic surveillance for cancer cells and that they do not increase the likelihood of problematic infections.

Basic science studies using established animal models of cancer and cancer-related symptoms will continue. Currently, animal models for pain are the best-developed and most useful for generating and testing hypotheses because mechanisms are more physiologically defined and behaviorally measurable for pain than for other symptoms. These studies are already progressing toward defining the cellular and molecular mechanisms by which immune activation or chemotherapy induces hyperalgesia in rodents.

The animal models of sickness behavior are fairly mature and will provide useful tools for addressing cancer symptoms. However, additional animal models of wasting/cachexia, fatigue, and cognitive impairment are needed. Current models labeled as representative of these symptoms may not correspond very well operationally or behaviorally to human symp-

toms. For example, human cognitive impairment often involves working memory rather than retentive/consolidative memory, but the rodent memory models commonly used may not actually test working memory. Animal models representative of fatigue are particularly lacking<sup>4</sup> and require careful attention to distinguish motivational deficits from fatigue. Expert panels composed of clinical and basic scientists could help to specify the operational definitions of components of human cancer symptoms and could propose component animal behaviors that might parallel these definitions.

The evolution of animal models of sickness behavior that parallel symptom expression in cancer patients, coupled with an increased understanding of the correlates and patterns of the expression of these symptoms, suggests that such symptoms are produced by common biologic mechanisms. The available evidence is consistent with the hypothesis that alterations in cytokines and other neuroimmunologic processes may be critical to both symptom production and, potentially, symptom treatment and prevention. Continued testing of this hypothesis and exploiting the leads that might arise will require a high level of integration of clinical and basic science efforts.

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