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The Reply:

The first paragraph of the letter by Van Houdenhoven et al (1) is unrelated to the article in the *Journal*, so we will refrain from comment. Moreover, the statements about the 50 patients have not been published in the scientific literature.

Some patients with chronic fatigue syndrome, as well as many healthy persons, have experienced severe burdening life events and chronic stress. These experiences should not preclude a diagnosis of chronic fatigue syndrome in patients who fulfill the Centers for Disease Control criteria. Indeed, the definitions of the syndrome by Fukuda et al (2) and Schluederberg et al (3) state that patients with a psychiatric history should not be excluded from the working definition of chronic fatigue syndrome.

It is clear that stress can influence the course of disease adversely, as in cancer for example, but do we treat stress instead of the biological correlates in cancer patients? In chronic diseases, coping strategies and psychological support are certainly very important. Although comprehensive rehabilitation programs are beneficial for most chronically ill patients, they do not solve the underlying problem nor do they deal with the cause of disease. The long-term outcome of comprehensive rehabilitation programs for patients with chronic fatigue syndrome remains unproven.

The authors assume that RNase-L dysfunction is inherently associated with a preceding viral infection. However, our observations suggest that while RNase-L may have an effect on chronic fatigue syndrome, they do not suggest that viruses, or a specific immune dysregulation, cause the syndrome. Chronic fatigue syndrome is probably a multifactorial syndrome that involves many dysregulations.

Hypothalamic-pituitary-adrenal axis disturbances do not fully explain the clinical picture of chronic fatigue syndrome. Many other central and peripheral hormonal systems (eg, the antidiuretic hormone and renin-angiotensin systems) can be abnormal in these patients. Perhaps there is a defective intracellular response to hormonal stimulation in target cells in these patients.

The statements on the etiological role of stress are based only on observational data. Identifying potential biological markers for chronic fatigue syndrome reminds us of the importance of demonstrating that stress-reduction therapies are effective in randomized controlled trials.

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The Reply:

Doctor Van Houdenhove and colleagues misunderstand my position. Since the beginning of our studies of chronic fatigue syndrome more than a decade ago, I have said that "with the chronic fatigue syndrome . . . it may be more productive to avoid the kind of 'mind-body' dualism that has characterized much past thinking about the pathogenesis of illness" (1). Moreover, in recent reviews (2,3), I have highlighted the possible effect of stress in making people vulnerable to this illness and the substantial evidence that hypothalamic dysfunction may be the mediator of such stress. Indeed, in the editorial that Dr. Van Houdenhove refers to, I cited a few of the most persuasive studies demonstrating hypothalamic dysfunction in patients with chronic fatigue syndrome.

Van Houdenhove and colleagues would have to concede, however, that many patients with chronic fatigue syndrome do not report unusual stressors in the months before the onset of their illness and do not have evidence of hypothalamic dysfunction. Available data do not support the hypothesis that stress leading to hypothalamic dysfunction explains all cases of chronic fatigue syndrome. It must be more complicated than that.

I agree with Van Houdenhove and colleagues that "all symptoms . . . have a 'real' (neuro)-biological basis," although that is a difficult proposition to prove. I also agree that the central nervous system and immune system communicate with one another. Indeed, it is plausible that the "immunological" phenomenon reported by DeMeirleir and colleagues is secondary to a primary process in the central nervous system.

In summary, the main point of my editorial was that there are objective, measurable, biological perturbations in many patients with chronic fatigue syndrome. In the face of that evidence, the suggestion that these patients are "imagining" their symptoms is unwarranted. The suffering of patients with chronic fatigue syndrome has a real, biological basis—just as Van Houdenhove and colleagues argue—and biologically ori-