

# Stress-Induced Immunomodulation

## Implications for Infectious Diseases?

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**T**HERE IS NOW SIGNIFICANT LITERATURE showing that psychological stress can down-regulate various aspects of the cellular immune response. It is also established that communication between the central nervous system and the immune system occurs through bidirectional signals linking the nervous, endocrine, and immune systems. Psychological stressors affect the immune system by disrupting these networks. In this overview, we discuss the implications of psychological stress-associated immune modulation and risk for infectious disease.

### Stress and Immune Function

At a molecular level, human immune function is mediated by the release of cytokines, nonantibody messenger molecules, from a variety of cells of the immune system, and from other cells, such as endothelial cells. We will not be discussing cytokine production by non-immune cells since they are not known to be related to the etiology or pathogenesis of immune-mediated disease.

These cytokines subsequently stimulate cellular release of specific compounds involved in the inflammatory response. Such biochemical alterations in immune function are, in part, induced by plasma hormone concentration changes elicited by a stressor subsequent to activation of the sympathetic nervous system and the sympathetic-adrenal medullary and hypothalamic-pituitary adrenal axes.<sup>1</sup> For instance, some of the immune changes can be ameliorated by pretreatment of experimental subjects with  $\beta$ -adrener-

gic antagonists.<sup>2,3</sup> Thus, the hormonal content of plasma, which in many cases is determined by activity of discrete areas of the brain (for example, the hypothalamus or locus coeruleus), can influence the activity of the immune system.<sup>4,5</sup>

The hormonal alterations induced by stress are responsible for the changes in cytokine concentrations because stress hormones alter the synthesis and release of the cytokines by leukocytes. Considerable information regarding the function of the immune system has been learned from *in vitro* studies. It is important to remember that *in vitro* studies are usually performed using tissue culture-growth media and are designed to optimally support the function of various leukocytes. Thus, there may be significant differences between the function of a given leukocyte when studied under ideal *in vitro* tissue-culture conditions and those that exist *in vivo* in which, for example, variable concentrations of cortisol and catecholamines are present. Therefore, the functionality of the immune system measured under ideal *in vitro* tissue-culture conditions is unlikely to be fully reflected in what occurs *in vivo*.

### Stress and Infection-Related Antigens

Animal models provide evidence to support the link between stress and infectious disease. For example, psychological stress such as crowding prior to and following tuberculosis infection affects the outcome of the infection.<sup>6</sup> It has been shown that social disruption in mice causes reactivation of latent herpes simplex virus.<sup>7</sup> Stress has also been shown to enhance reactivation of latent herpesviruses such as Epstein-Barr virus in human subjects.<sup>8</sup> Such data mean that stress should have measurable health consequences.

A rich literature also shows that psychological stress can inhibit many aspects of the immune response including innate immunity (eg, natural killer cell lysis), T-cell responses, and antibody production *in vivo* and *in vitro*.<sup>1</sup> While we have some understanding of how the immune system functions in normal and severely immunocompromised subjects, less is known regarding the degree of suppression of the immune system necessary to produce risk for severe infections. Because suppression of immune function does not necessarily indicate poorer health status or risk for disease among young and healthy adults, small immunological decrements do not provide clear information on health risk. To assess these effects, responses of chronically stressed populations, such as spousal caregivers of patients with Alzheimer disease, have been studied in comparison with nonstressed control subjects on immune indices including vaccine responses<sup>9</sup> and duration of wound healing.<sup>10,11</sup>

To determine whether chronic stress could influence the immune response to an influenza virus vaccine, Alzheimer disease caregivers and well-matched noncaregivers received the vaccine. Although participants in this study had similar vaccine histories, rates

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of chronic illnesses, and medication usage, caregivers had poorer cellular and humoral immune responses to the vaccine than controls.<sup>9</sup> This study was recently confirmed.<sup>12</sup> The data suggest that chronically stressed subjects may have deficits in their immune response to an important vaccine. The data also confirm 2 previous reports showing that acute stress can suppress the virus-specific antibody and T-cell responses to a hepatitis B vaccine.<sup>13-15</sup> These vaccination results are particularly relevant for older adults. Older adults who show poorer responses to vaccines also have higher rates of clinical illness including influenza virus infections.<sup>16</sup> Thus, the data may also provide us with a clue as to how stress could affect the immune response to a pathogen. Our inference is that a poor immunological response to vaccination has medical consequences.

Data exist on the role of stress in influencing host resistance to upper respiratory tract infections produced by exposure to 5 different strains of rhinovirus, to a strain of coronavirus, and to respiratory syncytial virus. After inoculation, the subjects were quarantined and monitored for 5 or more days to assess whether they developed infections and cold symptoms. Approximately one third of those subjects exposed to 1 of these viruses developed a serologically verified clinical illness.<sup>17</sup> In the first study, higher scores on questionnaires asking about stressful life events, perceptions of stress, and negative emotional experiences were associated with a greater likelihood of developing a clinical illness defined as cold symptoms concomitant with isolating infectious virus or developing a 4-fold increase in antibody titers.<sup>18</sup>

In a second study, a life-stress interview replaced the questionnaire. This technique allowed the specification of the types of stressful events that increase risk. These included chronic events (lasting a month or longer), especially chronic social conflicts and underemployment or unemployment.<sup>18</sup> Other plausible factors that

might be the cause of both changes in stress and greater susceptibility to disease, such as age, sex, education, and personality characteristics including self-esteem and personal control, were unable to account for these results. The results show that there is a relationship between psychological stress and susceptibility to several cold viruses.

### **Stress and Human Immunodeficiency Virus**

Studies have been performed to explore the possibility that stress might influence the pathophysiology of human immunodeficiency virus (HIV) infection. Attempts to find an association between stress and disease progression in patients with acquired immunodeficiency syndrome (AIDS) have met with conflicting results.<sup>19</sup> For example, in studies of a cohort in San Francisco, Calif, depression predicted CD4<sup>+</sup> T-lymphocyte decline<sup>20</sup> and mortality.<sup>21</sup> Analysis of the Multicenter AIDS Cohort Study failed to observe an association between depression and the decline of CD4<sup>+</sup> T lymphocytes, disease progression, or death,<sup>22</sup> but others have found significant associations between immunological parameters reflective of HIV progression and psychosocial factors, particularly denial and distress,<sup>23</sup> and concealment of homosexual identity.<sup>24</sup>

Obviously, studies of stress and the infection component of AIDS confront major methodological challenges. Among these is the need to distinguish between naturally occurring events such as bereavement, reactions to the illness such as active coping and concealment, and mood states that are often inexorably linked to a number of important disease-related variables, including emotional correlates of HIV-related symptoms. Perhaps the greatest challenge is to determine the proper measurement of disease progression in patients infected with a virus that strikes the immune system directly. Work performed, to date, has focused on CD4<sup>+</sup> T-lymphocyte levels, which could be markedly influenced by treatment. Excluding patients from treatment cre-

ates bias and correcting for treatment produces new variables that we are still trying to understand. More recently, the outcome variables have shifted to direct measures of viral load or viral burden. However, these measurements are highly variable in that virus can be undetected at various stages in the disease and can be markedly influenced by the new combination drug treatments. Indeed, efforts to study stress and disease progression in patients with AIDS may be subject to even greater challenges with new therapies.

### **New Directions for Study**

Although psychological stress alters the immune response, these changes have generally been small and within normal ranges.<sup>25</sup> Even so, high levels of chronic stress have been associated with an increased susceptibility to infectious disease. This has raised 2 significant areas that need further exploration. First, small changes in 2 or more parameters may increase the biological susceptibility to infectious disease to a far greater magnitude than a small change in a single parameter of immune function. It will be important for immunologists to define the significance of alterations in the function of the numerous interactive components of the immune system in order to clarify the clinical significance of tests of immune function. Second, the hormones that modify the function of the immune system need to be better characterized. As we learn more about these processes, we should also explore the possibility of optimizing hormonal concentrations in plasma in an attempt to promote immune system function.

Information on the impact of stress-induced changes in immune response and in risk for infectious disease is limited. However, data thus far support the hypothesis that the down-regulation or dysregulation of different components of the immune response associated with psychological stressors may have health implications with regard to infectious disease.

Outside of proven clinical interventions, there is reason to think that cer-

tain changes in lifestyle might increase host resistance to infectious diseases. These include broadening one's social involvements (eg, joining social or spiritual groups, having a confidant, spending time with supportive friends) and being more careful to maintain healthful practices such as proper diet, exercise, and sleep, especially under stressful conditions.<sup>26</sup>

Promoting behavioral modifications to healthy individuals who fail to adopt such behaviors and then de-

velop immunologically mediated diseases may create feelings of guilt with associated stress and immune suppression. Thus, careful study is needed regarding the obligation of physicians in advocating behaviors that may be beneficial to healthy individuals.

It is noteworthy that stress has also been associated with reports of both greater severity and prolongation of disease in patients with infectious diseases as well as other immune-mediated diseases. Stress reduction might also pro-

vide significant benefits to these patients. Thus, physicians should be encouraged to understand the role of stress in the pathogenesis of diseases such as infections, asthma, rheumatoid arthritis, multiple sclerosis, uveitis, inflammatory bowel disease, psoriasis, and cancer.

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