Psychoneuroimmunology and Health Consequences: Data and Shared Mechanisms

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There is evidence linking psychosocially mediated immunological alterations with cancer, infectious illness, and HIV progression. The data reviewed suggest that immune modulation by psychosocial stressors and/or interventions may importantly influence health status. The research literature also suggests that the impact of chronic stressors and psychosocial factors on sympathetic nervous system and endocrine function influences the immune system, thereby providing shared mechanisms that may impact on disease susceptibility and progression across a broad spectrum of disorders. A better understanding of individual vulnerability, such as occurs with aging, may help to pinpoint those at greatest risk.

Considerable evidence has accumulated demonstrating psychosocial or behavioral modulation of immune function. However, relatively few studies have simultaneously shown actual health changes in individuals with immunological alterations. The low incidence of clinical endpoints in many populations has provided a significant barrier to sufficient power to test hypotheses (1, 2).

Although stressed or depressed individuals may show immunological changes (3, 4), actual infectious disease episodes are a function of differential exposure to pathogens as well as the prior health of the individual, particularly in regard to immune system function. Furthermore, across individuals who have equal exposure to an infectious agent, e.g., a virus, the probability of developing a clinical illness, and the intensity and duration of an illness episode are dependent on the prior status of the individual's immune system.

Extending this rationale, those individuals who are presumably most likely to show health changes in response to stressors are those whose immune system function is already compromised to some degree, either by an immunosuppressive disease like AIDS, or by a natural process such as aging that is associated with immunological down-regulation. Poorer immunological defenses at the onset of a stressor could place these individuals at greater risk,

since smaller stress-associated immunological decrements could have more important consequences. In this vein, some evidence suggests that chronically distressed individuals may also be at greater risk because of longer term immunological changes (5, 6).

In this paper we will discuss evidence linking psychosocially mediated immunological alterations with cancer, infectious illness, and human immunodeficiency virus (HIV) progression. We will also speculate on possible shared psychosocial variables (e.g., chronic stressors, psychological state) and response mechanisms (i.e., sympathetic nervous system [SNS] reactivity, endocrine and immune changes) that may impact similarly upon the course of infectious diseases, cancer, and disorders associated with aging.

CANCER

Research that has attempted to link psychosocial stressors with tumor development or progression has faced many obvious difficulties (7). For example, stage of disease can have a profound effect on how patients feel, and cancer treatments such as chemotherapy and radiation are associated with a number of adverse side effects.

One obvious area of interest is the possibility of influencing the course of cancer through behavioral interventions. Properly designed intervention studies provide a powerful design for examining psychosocial factors; by random assignment of patients who have the same kind and stage of cancer to control and intervention conditions, researchers can assess psychological, immunological, and disease changes.

One of the best studies in this area evaluated both the immediate and longer term effects of a 6-week structured group intervention that consisted of health education, enhancement of problem-solving skills regarding diagnosis, stress management tech-

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niques such as relaxation, and psychological support (8, 9). The patients had stage I or II malignant melanoma and had not received any treatment after surgical excision of the cancer. The intervention patients were seen in groups of 7 to 10 patients who met for 90 minutes every week for 6 weeks. Note-worthy shorter term differences included reduced psychological distress and significant immunologi-cal changes in the intervention group patients, com-pared with the control group. The former showed significant increases in the percent of natural killer (NK) cells, an increase in NK cytotoxic activity, as well as a small decrease in the percentage of helper/inducer T cells. Most of these changes were not found at the 6-week follow-up point, emerging 6 months later. The majority of the intervention-group patients showed increases on these assays, and the magnitude of these changes was frequently greater than 25%. In contrast, only one third of the control patients showed these changes.

A 6-year follow-up of these patients showed a trend toward greater recurrence and a statistically significant higher mortality rate in control patients than in intervention patients (9). The group differ-ences remained significant after adjusting for the size of the initial malignant melanoma lesion, a key risk factor.

Consistent with results of the intervention study with melanoma patients, Spiegel and colleagues (10) showed that a year of weekly supportive group therapy sessions with self-hypnosis for pain was associated with extended survival time in women with metastatic breast cancer. The 50 women ran-domly assigned to the intervention group survived an average of a year and a half longer than the 36 control patients. The study's 10-year follow-up showed that divergence in survival began 20 months after the intervention had ended. Although these data may reflect immunological alterations that in-fluenced the course of the cancer, a number of other interpretations are plausible. As the authors note, patients in the intervention condition could have been more compliant with medical treatment, had better health behaviors such as exercise and diet. Such behavioral differences could contribute to the observed outcome.

INFECTIOUS ILLNESS

Response to Vaccines as a Model for Infection

Although animal studies are beyond the purview of this paper, animal models have clearly shown that stress operates as a cofactor in the pathogenesis and/or severity of infectious disease via alterations in immune system function (11–13). Although data from research with human subjects are more limited, studies that have exposed volunteers to antigens in the form of vaccines or deliberately infected subjects with pathogens such as cold viruses provide direct evidence that stress modulates the speed and po-tency of relevant immunological defenses. For exam-ple, we gave a series of three recombinant hepatitis B (Hep B) inoculations to 48 second-year medical students on the last day of a 3-day examination series to study the effects of academic stress on the students' ability to generate an immune response to a primary antigen (14). A quarter of the students seroconverted after the first injection; early serocon-verters were significantly less stressed and less anx-ious than those students who did not seroconvert until after the second injection. In addition, at the time of the third inoculation students who reported greater social support demonstrated a stronger im-mune response to the vaccine, as measured by anti-body titers to a Hep B surface antigen and the virus-specific T-cell (blastogenic) response to a viral peptide. These stress-related alterations in Hep B vaccine response have subsequently been replicated by another lab (15).

These data suggest that the immunological re-sponse to a vaccine can be modulated by a mild stressor even in young, healthy adults who have a long history of exposure (and mastery) for this very stressor, taking examinations. Most importantly, these data provide a window on the body's response to pathogens, such as viruses or bacteria. Inasmuch as the students who were more stressed and more anxious seroconverted later, these same individuals might also be slower to develop an antibody re-sponse to other pathogens; thus, they could be at greater risk for more severe illness.

Inoculation With Cold Viruses

Cohen et al. (16) assessed the effects of stress on susceptibility to colds by inoculating 357 volunteers with either a cold virus or a placebo. They found that rates of both respiratory infection and clinical colds increased in a dose-response manner with increases in psychological stress across five different cold viruses, providing a well-controlled demonstration of increased infection associated with increased stress. Their subjects fell between the ages of 20 and 55. Thus, their data are likely to significantly under-estimate the effect size for an older population.

Herpesviruses

Convergent animal and human data have linked stress and the appearance, duration, and intensity of herpesvirus infections (17). Unlike other common viruses such as rubella that are usually eliminated by the immune response after a period of time, individuals remain latently infected for life after infection with any of the herpesviruses. When cellular immunity is compromised (e.g., in patients with immunosuppressive diseases such as AIDS, or in patients undergoing immunosuppressive therapies like some chemotherapies), immunological control over herpesvirus latency is impaired. In some cases reactivation of the latent virus may occur and may result in disease. However, there are characteristic immunological alterations that can also occur in the absence of any symptoms, particularly *elevations* in antibody titers.

One study demonstrated that stressors may enhance susceptibility and severity of the primary infection. Kasl et al. (18) examined psychological and immunological data from West Point cadets who were seronegative (not latently infected) with Epstein-Barr virus (EBV, a member of the herpesvirus group) on entry into the academy. Data collected over the next 4 years showed that a triad of risk factors (higher levels of motivation for a military career, poorer academic performance, and having a father who was an "overachiever") was associated with three important illness indices: an increased risk for seroconversion (i.e., risk for infection), longer hospitalization in the infirmary after seroconversion (presumably reflecting more severe illness episodes), and higher antibody titers to EBV among those who seroconverted in the absence of clinical symptoms.

HIV

Because the human immunodeficiency virus (HIV) can latently infect lymphocytes, parallels between psychosocial mediation of latent herpesvirus infection and HIV have been proposed (2, 19, 20). Although several laboratories have attempted to relate psychological variables to immunological change and disease progression in people infected with HIV, the results have been mixed (1, 2, 20–25). Possible reasons for some null findings may be related to heterogeneity of subject populations on such key factors as disease stage, drug abuse history, gender, health behaviors, and age; in addition, some immunological measures may be more sensitive than others (22, 26). Disease stage seems to be a particularly important variable: HIV infection may be less influenced by psychosocial variables as the disease progresses (1, 22, 27).

Two studies examined the relationship between depression and rate of CD4 decline in HIV-infected men. Data from a cohort of 277 San Francisco-area men showed that depressed men had faster rates of decline in CD4 counts than nondepressed men: the former declined 38% faster than the latter (1). These differences in rate of decline were maintained after controlling for known physiological predictors of HIV progression, including antiretroviral medication use and baseline symptoms. In contrast, Lyketsos et al. (23) did not find that depressive symptoms were related to rate of CD4 decline in a cohort of 1718 men.

In an effort to address these differences, the San Francisco investigators conducted further analyses of their CD4 data. They noted that their mean baseline was $.641 \times 10^9$ cells/liter (1) compared to $.522 \times 10^9$ cells/liter in the men assessed by Lyketsos et al. (23). When the San Francisco sample was divided at the median ($.621 \times 10^9$ cells/liter), overall depression accounted for significant CD4 decline in men whose values were initially above the median, whereas men initially below the median did not show a similarly significant relationship. Moreover, they noted that the declines associated with depression in men with higher baseline CD4 cells were clinically significant: the effects were comparable with those of p24 antigenemia, ". . . the most powerful predictor of HIV progression" (p. 1743).

Kemeny and her colleagues compared men who had lost one or more close friends to AIDS in the prior year with men who had not. Higher levels of depressed mood were associated with lower numbers of CD4 cells and increased expression of activation markers in lymphocytes in nonbereaved men, but not in bereaved men, a pattern that replicated across two cohorts (2). She suggested that higher depression scores may represent different processes in the two groups (e.g., grief in the bereaved, depressed mood in the nonbereaved), and the two processes may have different immunological correlates. In additional work she found that men characterized by chronic and severe depression over a 2-year period demonstrated a sharper decline in CD4 cells than nondepressed men who were matched on age and CD4 levels at baseline (2).

Intervention work with HIV seropositive subjects has produced promising results. Five weeks before notification of their HIV serostatus, 50 gay men were randomly assigned to either aerobic training or a control group (28, 29). Subjects were assessed after the 5-week training period and 72 hours before notification of serostatus, with one additional assess-

ment a week after notification. The exercise intervention attenuated emotional distress and NK cell decrements after notification of positive serologic HIV status: anxiety and depression increased and NK cell numbers declined in seropositive control subjects after notification, whereas seropositive exercisers resembled both of the seronegative groups, with no affective or immunological change. Seronegative exercisers also showed a significant net increase in CD4 cells, although seropositive exercisers showed a smaller increase.

In parallel data from this investigative group, 47 asymptomatic healthy gay men were randomly assigned to either a cognitive behavioral stress management condition or an assessment-only control group, using the same 5-week period before notification of HIV antibody status as the exercise study (30). The seropositive behavioral intervention subjects showed significant increases in CD4 and NK cell counts, as well as a slight increment in the mitogen response of lymphocytes; as with the exercise study, there were no significant increases in depression after notification in the intervention subjects. In contrast, control subjects showed slight decrements in mitogen responsivity and lymphocyte cell counts from before to after notification. Relative to controls, subjects randomized to either the aerobic exercise or the cognitive behavioral stress management condition showed decreases in antibody titers to two latent herpesviruses, EBV and Human Herpesvirus 6 (31). There was some evidence that greater relaxation practice and greater willingness to comply with the intervention may have led to greater change.

A 2-year follow-up of 23 HIV seropositive men from this cohort showed that 9 had developed symptoms (including 5 with AIDS), and 4 of the 9 had died (22). After controlling for CD4 cell numbers at entry into the study, low adherence to intervention protocols and denial remained significant predictors of disease progression. Moreover, the research team also showed linkages among psychological variables, immunological data, and disease progression: denial correlated with a key measure of immunological status, CD4 cell numbers, at the 1-year follow-up, and CD4 cell numbers at the 1-year follow-up predicted disease progression at the 2-year follow-up.

Aging

Links between stress or distress and immunity could have even more potent health consequences for older adults, because immune function declines with age, particularly functional aspects of the cellular immune response (32–34); among adults over 75 years of age, pneumonia and influenza together are the fourth leading cause of death (35). Age-related immunological decrements are thought to be associated with the greatly increased morbidity and mortality from infectious illness in the elderly: poorer immune function has been associated with higher rates of mortality in individuals over 80 years of age (36). Importantly, older adults show greater immunological impairments related to depression than younger adults (37).

We assessed changes in depression, immunity, and health in a chronically stressed older population, spousal caregivers of Alzheimer's Disease (AD) victims (4). Caregivers had a substantially greater incidence of depressive disorders than sociodemographically matched control subjects. During the 13-month interval between the initial sample and the follow-up sample, caregivers showed decrements on three measures of cellular immunity relative to controls. Spousal caregivers who reported lower levels of social support at intake and who were most distressed by dementia-related behaviors showed the greatest and most uniformly negative changes in immune function at follow-up (4). Caregivers also reported that they had experienced more days of infectious illness, primarily upper respiratory tract infections.

SHARED MECHANISMS: LINKS AMONG SNS REACTIVITY AND ENDOCRINE AND IMMUNE FUNCTION

Recent studies of immune responses to brief experimental stressors have provided preliminary evidence that individuals who exhibit the largest sympathetically mediated increases in cardiovascular reactivity also show the largest catecholaminergic increases and immune changes (38–40). If sympathetic cardiac activation is a marker or determinant of longer term changes in immune function, then the cardiovascular, endocrine, and immune changes evoked by brief experimental stressors may help to illuminate the nature of the interactions among these physiological systems.

Importantly, preliminary evidence suggests that chronic stress may moderate cardiovascular reactivity, thus providing one possible mechanism through which chronic stress could modulate acute endocrine and immune change, as well as (speculatively) longer term changes. For example, chronic stress has been implicated as a factor in enhanced cardiovascular reactivity, elevations in catecholamines, and

272

down-regulation of immune function in several studies from Baum's laboratory (5, 41, 42). Similarly, we found that the chronic stresses of caregiving interacted with social support and age in modulating cardiovascular reactivity (43). Irwin et al. (44) found higher levels of neuropeptide Y (NPY), a sympathetic neurotransmitter released during emotional stress, in AD caregivers compared with controls. As described previously, caregivers have poorer immune function than controls (4, 6). Thus, chronic stressors also seem to produce longer term autonomic, immunologic, and endocrinologic alterations.

Individuals characterized by high cardiac sympathetic reactivity to acute psychological stressors show magnified cortisol and NK cell cytotoxicity responses to acute stressors, providing one mechanism for longer term immune modulation (40, 45). In addition, data from animal studies demonstrate that SNS activity also inhibits antigen processing and presentation (46).

Antigen processing and presentation has particular relevance for older adults. Consistent with other evidence of immune senescence, many older adults do not respond to vaccines (or other "new" antigens) as efficiently as younger adults (47). Older adults attain lower peak antibody levels after vaccination, and they show more rapid or steeper rates of decline than younger adults (48). A poorer immune response to influenza vaccine is associated with greater risk for influenza (49), as well as other respiratory infections (50). Thus, high sympathetic reactors may be a particular risk group for infectious illness, particularly among older adults. Clearly, a better understanding of these individual differences in response to stress could help identify those individuals who may be more prone to long-term health changes.

We have reviewed evidence linking psychosocially mediated immunological alterations with cancer, infectious illness, and HIV progression. There are now sufficient data to conclude that immune modulation by psychosocial stressors and/or interventions can lead to actual health changes. A better understanding of individual vulnerability will help to highlight those at greatest risk.

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