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PSYCHOSOCIAL MODERATORS OF IMMUNE FUNCTION

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ABSTRACT

This paper reviews evidence linking both major and minor stressful events to changes in immune function in humans. We suggest that declines in immune function are a very frequent concomitant of the heightened distress associated with even commonplace stressful events like academic examinations. Moreover, chronic stress does not appear to lead to adaptation to the level of well-matched comparison subjects. These data are consistent with epidemiological studies that have found greater morbidity and mortality in certain distressed populations.

INTRODUCTION

We will review evidence linking both major and minor stressors to changes in immune function in humans, with some brief references to relevant animal work. We suggest that declines in immune function are a very frequent concomitant of the heightened distress associated with even certain commonplace stressors; factors such as the duration and intensity of the stressor, the prior health of the individual (particularly with respect to immune system function), and recent exposure to pathogens are important in determining actual organic disease outcomes (1). In addition, psychological resources (e.g. feelings of control or supportive interpersonal relationships) that reduce distress also concurrently attenuate adverse immunological changes.

IMMUNE SYSTEM FUNCTION: INFORMATION AND ISSUES

The immune system has two limbs, the humoral immune system and the cellular immune system. The two arms have different functions. The activities of the humoral immune system are important for the defense against bacteria and viruses in body fluids; the production of immunoglobulins or antibody by B-lymphocytes is critical in this regard. The cellular immune response, the non-antibody producing arm of the immune system, is important for the defense against intracellular viruses, transplanted tissue, cancer cells, fungi, and protozoans.

To measure immune function, blood samples are obtained from subjects, and the numbers and/or functional abilities of various subgroups of white blood cells (leukocytes) or their biochemical mediators are assayed. There are a number of different subpopulations of leukocytes that have specialized functions, and no single assay or group of assays provides a standard, global measure of immunocompetence. However, since the functional activities of leukocyte subpopulations are interdependent, adverse changes in one subgroup can have multiple cascading effects.

While certain biochemical mediators of immune function may be synthesized in hours, significant changes in most leukocyte subpopulations are likely to occur over days. Considerably more time is necessary for certain types of cell replication, as well as alterations in the pre-existing numbers and types of cells. The longer time course for immunological changes (vs. other more labile systems such as hormones) has implications for stressor responsiveness. An isolated afternoon characterized by heightened distress is unlikely to have either statistically significant or biologically meaningful consequences for immune function. However, increased distress that is sustained over a period of several days to a week may well be associated with immunological decrements.

COMMONPLACE STRESSORS AND IMMUNE FUNCTION

Data from prospective studies suggest that even commonplace stressful events are associated with transient impairments in a number of immunologic functions. For example, significant declines in natural killer (NK) cell activity were found in blood samples obtained from 75 medical students during final examinations, in contrast to baseline samples collected one month previously; moreover, lonelier students (above the median on a loneliness scale) had significantly lower levels of NK cell activity (2). NK cell activity is thought to be important as a defense against cancer and certain viruses.

These immunological changes appear to be quite reliable across studies. For example, the significant drop in NK cell activity was replicated in two additional medical student samples (3,4). Moreover, two different and independent methods used to quantify the number of NK cells (vs. activity) also showed significant decrements: use of an NK cell monoclonal, and determination of the relative percentages of large granular lymphocytes, the NK cell phenotype (3).

A number of other immune functions also appear to be responsive to psychosocial influences. The percentage of helper T-lymphocytes was significantly lower in blood samples taken from 34 first-year medical students during an examination period, in contrast to baseline samples collected one month earlier (4). In addition, the frequency of relaxation practice in the half of the sample randomly assigned to a hypnotic-relaxation protocol was a significant predictor of helper cell percentages during examinations. Similar stress-related helper cell decrements were found in a sample of 40 second-year medical students during final exams (5). Helper T-cells stimulate the activities of a number of other types of cells (e.g. helper cells stimulate the production of antibody by B-lymphocytes).
The magnitude of immunological changes in response to commonplace stressors is sometimes dramatic. The production of interferon by stimulated lymphocytes plummeted from a mean of 2,000 µ/ml at baseline to 80 µ/ml during final exams in blood samples from 40 second-year medical students (3). Interferon is important because it is a major regulator of NK cells, stimulating their growth and differentiation, as well as enhancing their ability to destroy target (foreign) cells (6).

There are also very large changes in antibody titers to latent herpesviruses associated with academic stressors. Once infected with any of the five human herpesviruses, the host will remain latently infected for life. Elevated antibody titers to the latent herpesviruses are thought to reflect poorer cellular immune system control over the latent virus (e.g., patients on immunosuppressive therapies such as chemotherapy, or patients with immunosuppressive diseases such as AIDS have characteristically elevated herpesvirus antibody titers) (7).

Large changes were found in antibody titers to Epstein-Barr virus (EBV), a herpesvirus which is the etiologic agent for infectious mononucleosis (IM). The geometric mean titer (GMT) for virus capsid antigen was over 1:640 in blood samples drawn from 49 EBV seropositive (previously infected and still latently infected) medical students one month before and during final examinations (8). However, after the students returned from summer vacation in September, the GMT had dropped to 1:93, a level more consistent with the population mean of 1:80 described in seroepidemiological research (9). Lonelier students had significantly higher antibody titers to both this and another EBV antigen (8).

The proliferative response of lymphocytes cultured with a mitogen, a substance which stimulates cell replication, is thought to provide a model of the immune system’s ability to respond to infectious agents, such as bacteria or viruses. Data from this assay, called “blastogenesis,” showed a pattern similar to those described previously: during examinations, 40 medical students showed significantly poorer proliferation in response to two different mitogens than that measured six weeks earlier at baseline (5).

Since greater distress appeared to be associated with poorer cellular immunocompetence, we reasoned that reductions in distress might enhance immune function. Forty-five geriatric residents of four different independent living facilities were randomly assigned to one of three protocols: relaxation training, social contact, or no intervention. Subjects in the intervention conditions were seen individually three times a week for a month. Blood samples and self-report data were collected at baseline, at the end of the intervention, and at the one-month follow-up. Relaxation subjects showed a significant enhancement on two different assays of cellular immune function at the end of the intervention (greater NK cell activity, and lower antibody titers to a herpes simplex type I antigen), with concomitant significant decreases in distress-related symptomatology, in comparison to nonsignificant changes on these parameters in the other two groups. There was some global improvement across groups in the proliferative response of lymphocytes stimulated with a mitogen (10).

**IMPLICATIONS FOR OTHER COMMONPLACE STRESSORS**

To date, we have found significant changes during examinations on a variety of immunological assays used in our prospective studies with medical students; not surprisingly, distress is reliably higher during the examination periods. We do not have any evidence suggesting that our volunteers are somehow different in important ways from their classmates. There have not been even marginally significant differences between our volunteers and their classmates when we have regularly compared grades or personality test data (2,4).

Since variations in nutrition and sleep might influence immune function, we have assessed changes in weight and sleep. There have not been significant correlations between the immunological values and the minor weight changes or sleep deficits. In more recent work we have included several biochemical nutritional assays with relatively longer (two to three weeks) and shorter (eight days) half-lives, to assess the possibility that the changes in immune function simply reflected underlying nutritional changes. Since nutritional deprivation has adverse effects on immune function (11), the values for the plasma protein markers have been well within normal limits during both baseline and examination periods.

The immunological changes during exams are particularly noteworthy when viewed in the context of prior stressor exposure: these students were selected for medical school largely on the basis of their prior examination performances. Despite their long histories of success with this very stressor, they still show reliable drops in immunocompetence.

The heightened distress regularly found in our medical student samples during examinations is probably quite comparable to that elicited by other commonplace events. For example, certain deadlines for completion of major work projects occur with some frequency, and yet continue to be associated with considerable dysphoric arousal (e.g., for academicians, the deadline(s) for completion of grant proposals or the several days preceding a grant site visit are often accompanied by rather frenzied activity, coupled with recurrent concerns about the outcome of the upcoming evaluation). If the quality and intensity of emotional arousal in these situations is comparable to that of medical students during examinations, then similar immunologic changes may be expected.

**MORE INTENSE DISTRESS AND IMMUNE FUNCTION**

The increased distress generated by commonplace stressful events like examinations is reliably associated with poorer immune function. In addition, it appears that distress-reducing interventions may enhance at least certain aspects of immune function under certain conditions. Given these data, it is reasonable to expect that more intense or sustained dysphoria may also be associated with poorer immunocompetence.

Not surprisingly, clinically significant levels of dysphoria are associated with poorer immunocompetence. Across most studies, depressed patients have poorer immune function than nondepressed controls. For example, depressed inpatients have a poorer proliferative response to mitogen stimulation (12), and a lower percentage of helper T-lymphocytes (13). It has been suggested that the degree of immunosuppression may be related to the severity of depression (12).

Elevated herpesvirus antibody titers in psychiatric patients have also been reported in comparisons with nonpsychiatric controls, leading researchers to suggest that it might have a pathophysiologic role (14,15). However, it seems more likely that the
DISTRESS AND CARCINOGENESIS

Exposure to carcinogens is ubiquitous. For example, pesticide residues may be found in different kinds of fresh produce. Nitrites are found in many processed meats, some types of beer, and spinach. Sunlight, gamma rays, and x-irradiation all provide different kinds of radiation exposure. However, most carcinogen exposure is at low doses and for limited amounts of time.

Most carcinogens appear to induce cancer by damaging the DNA in cells, thereby producing mutant cells (16). The body’s defenses for dealing with carcinogen damage include enzymes that destroy chemical carcinogens, processes for identifying and repairing damaged DNA, and the destruction of mutant or unrepaired DNA by the immune system (17). The processes for repair or destruction of damaged DNA are quite critical, since faulty DNA repair is associated with an increased incidence of cancer (16).

The possibility of a linkage between emotional distress and carcinogenesis was explored in work using blood samples obtained from 28 nonpsychotic, nonmedicated psychiatric admissions (18). These inpatients were divided into high and low distress subgroups using a median split on their MMPI scale 2 (depression). Subjects’ leukocytes were exposed to x-irradiation to damage cellular DNA. The more depressed inpatients showed significantly poorer repair of damaged DNA, in comparison to their less depressed counterparts.

Given the cross-sectional nature of these data, however, it was possible that the depression-related deficits in DNA repair might simply be a function of a third variable (e.g. there might be a common genetic component for both depression and poorer DNA repair). Therefore, another study was designed to explore the possibility that stress would impair one component of the DNA repair process. Forty-four rats ingested the carcinogen dimethylacetamide, and half were assigned to a rotational stress condition. The levels of methyltransferase, an important DNA repair enzyme induced in response to carcinogen damage, were significantly lower in splenic lymphocytes from the stressed animals. The data are consistent with the depression-related deficits in DNA repair found in psychiatric patients, and suggest that stress may alter the DNA repair process (19).

It is important to consider the stress-related DNA repair deficits in light of the previously discussed decrements in NK activity during examinations. Taken together, these data suggest that stress might have direct effects on carcinogenesis through alterations in DNA repair, as well as indirect effects, through the poorer destruction or elimination of mutant cells.

PROLONGED EXPOSURE TO A STRESSOR

Using high intermittent noise with rodents over a period of 45 days, Monjan and Collector (20) found that the “acute” effects of the stressor (i.e. within the first week to ten days) were immunosuppressive, with lower mitogen responsiveness than found at baseline. However, mitogen responsiveness rose above baseline levels somewhere between days ten and twenty, leading to the suggestion that chronic stress might produce an enhancement in immune function. There are related data on the growth of implanted tumors in mice (21).

These and related rodent studies have led to speculation about the potentially positive effects of chronic stress on immune function. While both humans and rodents are mammals and there are many similarities in immune function, there are also important differences, particularly in the greater sensitivity of rodents to the immunosuppressive effects of the adrenal glucocorticosteroids (22). Furthermore, these rodent studies have used physical stressors, and adaptation to physical stressors may follow a different course than adaptation to the cognitive stressors of interest in human research.

Moreover, although it is certainly possible that some adaptation to repeated stressor exposure does occur over time, examinations still regularly evoke distress and the associated mild and transient impairments in immune function in most of our students, as was discussed earlier. There are also data suggesting that immunosuppression still occurs even after several months of longer-term stressor exposure. Husbands of women who had advanced breast cancer were studied prospectively, beginning one to two months before bereavement. Blastogenic data obtained one to two months after the wife’s death were still significantly lower than pre-bereavement levels (12).

The rodent data linking longer-term stressor exposure to immunoenhancement also contrast with data from separated/divorced women and married women. Marital disruption is consistently associated with greater morbidity and mortality than found in comparable married samples; for example, divorced individuals have six times the number of deaths from pneumonia as married individuals (23), and separated women have 30% more acute illnesses and physician visits than married women (24). Separated and divorced individuals are also significantly more distressed than their married counterparts, on the average (25). However, unhappily married individuals are more distressed and describe their health as poorer than either divorced or happily married people of the same race, sex, and age (26).

In order to examine psychological and physiological mediators of these effects, we obtained blood samples for immunological and nutritional analyses and self-report data from 38 separated/divorced women and 38 sociodemographically-matched married women (27). Poorer marital quality was associated with greater distress and a poorer response on three qualitative measures of immunity among married subjects. The 16 women who had been separated a year or less had significantly poorer immune function than their married counterparts. Among the entire separated/divorced cohort, greater attachment to the (ex)husband and shorter separation periods were associated with poorer immune function and greater distress. These data are consistent with the epidemiological evidence reviewed above.

DISTRESS, MORBIDITY, AND MORTALITY

If greater distress is associated with poorer immune function, then individuals in other distressed populations could be more susceptible to infectious disease (and perhaps cancer), recovery times after infection might be longer, and there could be greater mortality associated with some diseases. There are other data consistent with these premises.

In a recent year-long study of medical students, we found that examination periods were reliably associated with poorer immune function and greater distress, as we had shown previously. However, we found an increase in the incidence of infectious disease associated with examination periods as well (28).
Psychosocial Moderators of Immunity

One excellent seroepidemiological study suggested a longer-term association between the development of infectious mononucleosis and certain psychosocial risk factors. West Point cadets who had never had an acute EBV infection (i.e. they were EBV seronegative) were followed prospectively for four years (29). Both length of hospitalization for clinical infectious mononucleosis and elevated antibody titters among seroconverters without incapacitating clinical symptoms were associated with the interaction of the same psychosocial risk factors: high motivation for a military career coupled with a relatively poor academic performance. Greater unhappiness was associated with poorer control of latent herpesviruses in two other studies which did not include immunological measures (30,31).

Patients with trenchmouth, an infection associated with normally nonpathogenic indigenous oral bacteria, had poorer immune function than healthy controls. The patients also had significantly higher levels of depressive symptomatology, anxiety, and more recent negative life events than controls (32).

Consistent with the psychoimmunological research using bereaved and psychiatric patients are epidemiological studies that suggest these groups have significantly higher rates of morbidity and mortality (33-36). Unfortunately, many of these studies do not address the cause of death, so it is not always possible to examine immunologically-related causes of mortality.

Other research suggests that both psychiatric patients and bereaved spouses also have a greater incidence of cancer mortality than the general population (35,36). One 17-year prospective study that used over 2,000 nonpsychiatric men and controlled for a number of risk factors showed a significantly higher incidence of cancer associated with higher MMPI depression scores (37); these data are consistent with the depression-related differences in DNA repair described earlier (18,19).

INTEGRATING RESEARCH FINDINGS

Despite the large number of studies which have been published, the evidence for a causal relationship between stressful events and impaired health is not impressive. Within the life-change literature, correlations between the number of weight of life events and self-reports of health are most often in the .30s or lower (38). Data from the relatively few studies with objective health assessment procedures suggest that only a minority of individuals develop some organic disease. However, higher numbers of life events are regularly associated with greater distress (38).

Heightened and sustained distress is likely to be associated with at least transient immunosuppression. It is likely that differential exposure to pathogens and the prior health of the individual (particularly with respect to immune function) contribute to the propensity to develop an infectious disease. A variety of psychological resources may influence stressor appraisal or coping patterns, and thus may attenuate distress; in this way they may have an impact on associated changes in immune function, and ultimately on health.

Distress-related immunosuppression may have more important consequences in older adults with pre-existing age-related decrements in immune function (39), in individuals whose health already impaired, in patients with immunosuppressive diseases (HIV-1), individuals exposed to an infectious agent or carcinogen, or in individuals who have undetected tumor cells. In these and other at-risk groups, emotional distress may make some contribution to morbidity and mortality.

REFERENCES


