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Psychological influences on immunity

ABSTRACT: Epidemiologic studies link greater distress with increased morbidity and mortality. Both major and minor stressful events may alter immune function in humans. Conversely, distress-reducing interventions such as relaxation may enhance some aspects of immune function. The authors review the relationship between stressful life events, depression, and measured changes in immune function. They also examine the evidence for a relationship between distress and carcinogenesis.

Clinicians have long suspected that both major and minor stressful events may affect immune function. Informal observations and case reports have linked severely stressful life events with the sudden onset or worsening of cancer or other illnesses in which it is thought that immune factors may play a role. Only in recent years, however, have more scientific attempts begun to succeed in finding measurable links between stressful situations and changes in the immune system.

Major life events, depression, and immune function

Growing evidence¹ indicates that the distress that frequently accompanies major negative life changes may lead to alterations in immune function. For example, bereavement has been associated with immunologic impairments. In one prospective study,² blood samples were collected from 15 men, whose wives had advanced breast cancer, before and after death of the wives. Lymphocytes from these husbands showed a poorer blastogenic

response after their wives' deaths than before bereavement. Blastogenesis, the proliferative response of lymphocytes cultured with a mitogen, is thought to provide a model of the immune system's ability to respond to infectious agents.

In a cross-sectional study³ of marital disruption, we found that women who had separated from their husbands within the last year had significantly poorer immune function than demographically-matched married women. The separated and divorced women had significantly poorer responsiveness to two mitogens than the married women, as well as lower percentages of helper T-lymphocytes. Helper cells stimulate the production of antibody by B-lymphocytes, and they also stimulate the activities of a number of other types of cells.

The separated and divorced women also had significantly higher antibody titers to Epstein-Barr virus (EBV), a herpesvirus that is the etiologic agent for infectious mononucleosis (IM). Elevated antibody titers to the latent herpesviruses are thought⁴ to reflect poorer cellular immune system control over the latent virus; eg, patients

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Immunity

on immunosuppressive therapies or with immunosuppressive diseases such as AIDS have characteristic elevated herpesvirus antibody titers.

Within the group of married women, a poorer state of the marriage was associated with greater depression and a poorer response on three qualitative measures of immune function (blastogenesis with each of two mitogens, and antibody titers to EBV). In addition, data from the separated and divorced women showed that shorter separation periods and greater continued attachment to the former husband were associated with poorer immune function and greater depression.³

Clinically significant levels of depression are associated with poorer immunocompetence in psychiatric populations. Across most studies, depressed patients have poorer immune function than nondepressed controls. For example, depressed inpatients have a poorer blastogenic response than nondepressed controls.^{5,6} In other research,⁷ depressed patients have had lower percentage of helper T-lymphocytes than nondepressed controls. The degree of immunosuppression may be related to the severity of depression.⁶

Elevated herpesvirus antibody titers in psychiatric patients have also been reported⁸ in comparisons with nonpsychiatric controls, leading researchers to suggest possible etiologic connections. However, given the large stress-related changes in herpesvirus antibody titers found in normal populations,^{3,9} it seems more likely that the data reflect poorer control of the latent herpesviruses by the cellular immune system as a concomitant of the psychiatric patient's significantly greater dysphoria.

Commonplace stressful events, relaxation, and immune function

Certain commonplace stressful events are reliably associated with transient

impairments in a number of immunologic functions. For example, in contrast to baseline samples collected one month previously, significant declines in natural killer (NK) cell activity were found¹⁰ in blood samples obtained from 75 medical students during final examinations; moreover, lonelier students had significantly lower levels of NK cell activity. NK cell activity is thought to be important as a defense against cancer and certain viruses. These NK changes are quite reproducible across studies; the sig-

Some evidence indicates that more distressed populations are more susceptible to infectious disease and cancer.

nificant drop in NK cell activity was replicated in two additional medical student samples.^{11,12} Furthermore, 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 antibody, and determination of the relative percentages of larger granular lymphocytes, the NK cell phenotype.¹¹

Interferon is a major regulator of NK cells, stimulating their growth and differentiation, as well as enhancing their ability to destroy target (foreign) cells.¹³ The production of interferon by stimulated lymphocytes plummeted from a mean of 2000 U/mL at baseline to 80 U/mL during final exams in blood samples from 40 second-year medical students.¹²

Other immunologic changes have been observed in response to psychosocial stressors. In contrast to values from baseline samples collected one month earlier, the percentages of

helper T-lymphocytes were significantly lower in blood samples taken from 34 first-year medical students during an examination period.¹² Moreover, half of the sample was randomly assigned to a hypnotic-relaxation protocol, and the frequency of relaxation practice in these subjects 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 examinations, as compared with baseline values.¹⁴

The geometric mean titer 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. However, after the students returned in September from summer vacation, the GMT had dropped to 1:93, a level more consistent with the population mean of 1:80 described in seroepidemiologic research. Lonelier students had significantly higher antibody titers to both this and another EBV antigen.⁹

Bearing in mind the association between distress and 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. Individuals 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. Compared with nonsignificant changes in the social contact and no intervention groups, relaxation subjects showed a significant enhancement on two different as-

says of cellular immune function at the end of the intervention (greater NK cell activity and lower antibody titers to a herpes simplex type 1 antigen), with concomitant significant decreases in distress-related symptomatology. The proliferative response of lymphocytes stimulated with a mitogen showed some improvement across groups.¹⁵

We have found significant changes during examinations on most immunologic assays used in our prospective studies with medical students; in addition, distress is reliably higher during the examination periods. The subject groups have been drawn from five different medical student classes. There is no evidence suggesting that our volunteers differ from their classmates in important ways. We have regularly compared grades, and there have not been even marginally significant differences between our volunteers and their classmates; we also failed to find differences when personality test data from volunteers and their classmates were compared.^{10,12}

Changes in weight and sleep have also been assessed, because these parameters might influence immune function. Consistent significant correlations have not been found between the immunologic values and the minor weight changes or sleep deficits. Since nutritional deprivation has adverse effects on immune function,¹⁶ in more recent work we have included several biochemical nutritional assays to assess the possibility that the changes in immune function simply reflected underlying nutritional changes. The assays have included those with relatively longer (two to three weeks) and shorter (eight days) half-lives, and the values for the plasma protein markers have been well within normal limits during both baseline and examination periods.

The heightened stress regularly

found in our medical student samples during examinations is probably quite comparable to stress elicited by frequently experienced everyday events, eg, the several days of intensified activity that frequently precede vacations. If emotional stress in these situations is comparable to that of medical students during examinations, then similar immunologic changes may be expected.

Distress and carcinogenesis

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

Carcinogens appear to induce cancer by damaging cellular DNA, thereby producing mutant cells.¹⁷ The damage can be limited by enzymes that destroy chemical carcinogens, by certain processes for identifying and repairing damaged DNA, and by the destruction of mutant or unrepaired DNA by the immune system. These processes for repairing or destroying damaged DNA are quite critical, since faulty DNA repair is associated with an increased incidence of cancer.¹⁷

We utilized blood samples obtained from 28 nonpsychotic, nonmedicated newly admitted psychiatric patients to explore possible linkage between emotional distress and carcinogenesis.¹⁸ A median split on the Depression Scale of the MMPI (Minnesota Multiphasic Personality Inventory) was used to divide these inpatients into high and low distress subgroups. After leukocytes from these patients were exposed to x-ray irradiation in order to damage cellular DNA, we

found that the more depressed patients had significantly poorer repair of damaged DNA, compared with their less depressed counterparts.

It was possible that the depression-related deficits in DNA repair might simply reflect the common influence of a third variable, eg, there might be a common genetic component for both depression and poorer DNA repair. To investigate the possibility of a causal association between distress and impairments in DNA repair, another study¹⁹ was designed to assess the effects of stress on one component of the DNA repair process. Rats were given the carcinogen dimethylnitrosamine, 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 spleens from the stressed animals. These data provide further evidence that stress may alter the DNA repair process. In regard to the stress-related changes in NK activity, 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. The actual contribution of psychosocial factors to cancer incidence may be small, based on such factors as the heterogeneity of cancers and the evidence for genetic predispositions for certain malignancies.

Morbidity and mortality

Although the data are limited, some evidence indicates that more distressed populations are more susceptible to infectious disease and cancer, that recovery times after infection are longer, and that greater mortality is associated with some diseases. For example, we recently found²⁰ an association between periods of stress-related immunosuppression and episodes of

Immunity

acute infectious disease in medical students. A seroepidemiologic study²¹ 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 (ie, they were EBV seronegative) were followed prospectively for four years. Both length of hospitalization for clinical IM and elevated antibody titers among seroconvertors 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.

Epidemiologic studies^{22,23} of distressed populations such as bereaved and divorced adults and psychiatric patients suggest that these groups have significantly higher rates of morbidity and mortality. Moreover, psychiatric patients and divorced and be-

reaved spouses also have a greater incidence of cancer mortality than the general population.^{24,25} One 17-year prospective study²⁶ that used over 2,000 nonpsychiatric male subjects and controlled for a number of risk factors showed a significantly higher incidence of cancer associated with higher MMPI depression scores, consistent with the DNA repair data described earlier.^{18,19} However, other studies have failed to find consistent evidence of psychosocial relationships to the incidence of cancer.²⁷

Integrating research findings

Transient immunosuppression can be produced by heightened and sustained distress. Psychological resources such as supportive interpersonal relationships may influence the way individuals respond to stressful events, and thus may attenuate distress; in this way they may have an impact on associated changes in immune function,

and ultimately on health. The propensity to develop an infectious disease is likely to depend on differential exposure to pathogens and the prior health of the individual, particularly with respect to immune function.

Distress-related immunosuppression may have its most important consequences in individuals with preexisting decrements in immune function. Within this framework, at-risk groups may include older adults,²⁸ individuals whose health is already impaired, patients with immunosuppressive diseases such as AIDS, or individuals who have been exposed to an infectious agent or carcinogen. It is possible that emotional distress may make some contribution to morbidity and mortality in these and similar groups. □

Work on this article was supported in part by grant 1-R01-MH40787 from the National Institute of Mental Health.

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