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ABSTRACT

This review addresses the importance of studies of human psychoneuroimmunology in understanding the role of psychological factors in physical illness. First, it provides psychologically and biologically plausible explanations for how psychological factors might influence immunity and immune system–mediated disease. Second, it covers substantial evidence that factors such as res

influence both cellular and humoral indicators
Third, at least in the case of the less serious infe
herpes), it considers consistent and convincing
and negative affect and disease onset and progr
development, research also suggests a role of
mune diseases. Evidence for effects of stress, c
on onset and progression of AIDS and cancer is
possibly owing to methodological limitations in
illnesses, or because psychological influenc
magnitude or type necessary to alter the body's
missing in this literature, however, is strong
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ence of chemicals called cytokines that are produced by the immune system, cross the blood-brain barrier, and alter the function of the CNS (review in Rabin et al 1989). An important step in establishing that the CNS and immune system interact was accomplished by psychologists working with animal models who demonstrated that immune system change could be induced by classically conditioned stimuli (review in Ader & Cohen 1993).

The interests of psychoneuroimmunologists working with humans overlap with those of animal researchers, but human psychoneuroimmunologists' emphases are different.ı˝1b

ENUMERATIVE TESTS The enumerative assay most often used

ability to attach to a specific antigen, mark it for destruction, and prevent it from causing infection. Ab is produced in response to the herpes viral replication, and the amount of Ab produced fluctuates in relation to the amount of virus produced. Hence higher levels of herpesvirus Ab are interpreted as indirect evidence of compromised cellular immune function.

A more direct test of cellular immunity is the delayed-type hypersensitivity response. In this test, small amounts of antigen are introduced by injection into the skin. A hypersensitivity response is one in which swelling and redness occur at the site of injection. The inflammation is generated by the reaction of the antigen with antigen-specific T lymphocytes. Inflammation is expected in response to the antigens, and the larger the inflammation, the more "competent" the cellular immune system is assumed to be.

Finally, in an in vivo test assessing the competence of the humoral arm of the immune system, individuals are inoculated with an antigen, and the amount of Ab produced in response to that specific antigen is quantified. Depending on the specific type of Ab, it can be quantified from either blood or mucosal secretions (e.g. saliva, nasal discharge). The more Ab produced in response to an antigen, the more "competent" the humoral system is assumed to be.

Immunity and Disease

The immune system's defense against invading microorganisms is composed of a complex cascade of events. Moreover, the exact nature of any given immune response varies with the invaded organism's history of exposure, the type of antigen, and the route of entry into the body. Practically, human PNI researchers are limited to assessing a small number of rough markers of immune function rather than anything that resembles a true estimate of the body's ability to resist disease. For these and other reasons addressed later (see the section entitled "Do Psychological Factors Influence Immune System–Mediated Disease?"), PNI studies with immune (but not disease) outcomes are informative about the interrelation among behavior, the CNS, and the immune system, but do not necessarily indicate changes in resistance to disease. In the sections that follow, we first discuss studies on the relations between psychological factors and immunity, and then studies of the

HOW

also influence immunity. For example, persons experiencing negative affect often engage in poor health practices, such as smoking, poor dietary practices, and poor sleeping habits (Cohen & Williamson 1988), which may have immunosuppressive effects (Kiecolt-Glaser & Glaser 1988).

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events in immune regulation as well as suggest the benefit of positive events in health outcomes.

Two studies explored the impact of perceived stress on the body's ability to produce antibodies (develop immunity) in response to the standard series of three hepatitis B vaccinations. Glaser et al (1992) did not find a prospective relation between negative affect and seroconversion (initial production of hepatitis B antibodies) in response to the first injection. They did, however, find that those who did not seroconvert were more stress reactive (reported more stress in response to a subsequent exam period) than those who seroconverted. In contrast, Jabaaij et al (1993) found that greater perceived stress assessed after the second hepatitis B vaccination was associated with less antibody production (among those who seroconverted) in response to the third injection. It is unclear, however, whether these differences in antibody level are great enough to influence the degree of protection against infection provided by the vaccination.

Stressful events that last for a longer term, e.g. months or even years, have similar potential to influence the immune system. One example is the set of studies assessing stress effects on residents of the

exams. The intervention did not influence stress-induced changes in cellular immune function (Kiecolt-Glaser et al 1986). In a second study of relaxation training in medical students, neither the training nor immune measurement coincided with a common stressful event (McGrady et al 1992), but researchers did find increased lymphocyte proliferation in response to PHA and Con A in the relaxation group following the four-week intervention. Finally, elderly adults residing in a geriatric care facility who were trained in relaxation techniques showed improved cellular immune response, including increased NK activity and decreased levels of herpes antibody (Kiecolt-Glaser et al 1985). Work on relaxation training as a stress-reducing intervention is inconclusive. However, the literature suggests that relaxation training may be sufficient to temporarily alter the relation between usual background levels of stress and immune response, but not sufficient to influence stress-induced perturbations in immunity caused by external stressors.

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The correlations between sympathetic and immune response suggest that stress-elicited SNS response may drive the immune changes. However, this evidence is merely correlational and does not establish a causal chain.

Two recent experimental studies have attempted to provide evidence that would allow a causal inference regarding the mediating role of the SNS in the relation between acute stress and immune change. These studies are similar to earlier work in that persons exposed to stressors are compared to those not so thettudies are unalsnt

PWM; lowered NK activity; higher numbers of circulating white blood cells (primarily neutrophils and monocytes); and lowered numbers of NK, B, T, helper T, and suppressor/cytotoxic T cells (Herbert & Cohen 1993a). Longitudinal data also suggest that when people recover from depression, decreased NK activity is no longer evident (Irwin et al 1992). The relations between depression and immune outcomes are strongest in both older and hospitalized samples. However, it remains unclear whether this is because these groups suffer from more severe depression or whether age or hospitalization otherwise moderate the relation between depression and immunity.

Although these findings are reliable across studies included in the meta-analysis, there is variability in results. One reason for the variability is methodological: Few research groups have achieved high-quality designs. To limit variability, patients must be assessed when they are drug free, they must be carefully age- and sex-matched with comparison subjects, and appropriate controls must be used to deal with the day-to-day variability of immune assays (Schleifer et al 1993). One study, now a classic, that achieved these goals is also one of the largest and most carefully controlled studies of clinical populations to date. Schleifer et al (1989) found that, consistent with the meta-analysis, depression was associated with immunosuppression primarily among older patients and hospitalized patients.

As discussed earlier, relations between depression and immunity may sometimes be attributable to behavioral factors. Depressed persons sleep less, exercise less, have poorer diets, smoke more, and use alcohol and other drugs more often than do nondepressed persons (Gregory & Smeltzer 1983, Grunberg & Baum 1985). Although many studies now focus on physically healthy, drug-free subjects, relations between health behaviors and depression or immunity are generally not assessed. The few studies that included statistical controls for health practices such as weight and recent weight loss (Schleifer et al 1989), cigarette use, and alcohol consumption (Irwin et al 1987, 1990) suggest that these health practices do not account for alterations in immune function among depressed persons.

MOOD What do we know about the relation between normal fluctuations in mood and immune response? Relatively little. Moreover, most studies address relations between negative mood states and immunity, with only scattered work addressing the role of positive moods. A recent meta-analysis of this literature suggests that depressed mood in nonclinical samples is associated with decreased proliferative responses to mitogens and decreased NK activity (Herbert & Cohen 1993a). However, the effect sizes are considerably smaller (in fact, about half the size) than those found for clinical depression. Only a handful of studies investigate relations between anxiety and immunity. These studies found

that anxious mood is associated with decreased NK activity (Locke et al 1984) and decreased proliferative response to both PHA and Con A (Linn et al 1981).

Several studies examine the associations of positive and negative mood states with immune outcomes. For example, a daily diary study examined the relations between positive and negative mood states and antibody response to an orally ingested novel antigen over eight weeks (Stone et al 1987). Antibody levels were higher on days when respondents reported high positive mood states and lower on days when they reported high negative mood states. These results were replicated in a subsequent study that monitored mood and antibody levels over a 12-week period (Stone et al 1994).

In a handful of experimental studies, specific affective states were induced in healthy subjects and the subsequent acute immune changes were documented. For example, Knapp et al (1992) had subjects recall positive and negative experiences to induce "positive" and "negative" mood states. Both positive and negative moods were associated with decreased proliferative responses to PHA and increased numbers of neutrophils. Similar immune effects of positive and negative mood were attributed to the fact that all subjects reported increased levels of excitement (arousal) during the mood inductions, regardless of the valence of the mood.

Futterman et al (1994) used actors in a within-subjects design and induced mood using written scenarios that depicted four different emotional states: high-arousal positive, high-arousal negative, low-arousal positive, and low-arousal negative. Although NK activity was not associated with mood condition, the proliferative response of lymphocytes to PHA was differentially sensitive to mood valence. That is, proliferation increased following positive moods and decreased following negative moods.

Thus different moods may be associated with different immune responses. Clear interpretation of this work is impeded by a lack of consensus on the dimensions in which mood should be classified. However, existing work suggests that the dimensions of valence and arousal may be important ones in relating moods to immune function.

Interpersonal Relationships

Substantial evidence implicates interpersonal relationships in the maintenance of health (Cohen 1988, House et al 1988). A series of prospective studies shows that belonging to a strong social network is associated with longevity (reviewed by House et al 1988) and that perceptions of available support protect persons from the pathogenic effects of stressful events (reviewed by Cohen & Wills 1985). What is not clear, however, is the extent to which these effects are mediated by support-induced changes in immune function. Recent studies of loneliness, separation and divorce, perceptions of support, and

closure of traumatic events have begun to elucidate the impact of interpersonal relationships on immunity and immune system–mediated illness.

In their studies of first-year medical students, Kiecolt-Glaser and Glaser (Glaser et al 1985a, Kiecolt-Glaser et al 1984) found that persons higher in self-reported loneliness had lower NK activity and higher levels of herpesvirus antibody than those who described themselves as less lonely. In a related study, lonelier psychiatric inpatients had poorer NK cell function and lower proliferative responses to PHA than did patients who reported less loneliness (Kiecolt-Glaser

so severe that the relatively small effects of social support on immune function might be undetectable.

Many of the beneficial health effects of interpersonal relationships are attributed to receipt or availability of emotional support—someone to talk to about problems (Cohen & Wills 1985). A related literature has examined the potential health benefits associated with persons' disclosure of traumatic events. Pennebaker and his colleagues (Pennebaker & Beall 1986) reported that college students instructed to write about both the emotions and facts associated with a traumatic event had fewer subsequent visits to the health center than those instructed to write about emotions or facts alone. In a follow-up study of the role the immune system might play in the beneficial process of trauma disclosure (Pennebaker et al 1988), 50 healthy undergraduates were assigned to write about either personal and traumatic events or trivial topics. They wrote for 20 minutes a day on four consecutive days. Immunologic data were collected before the study began (baseline), at the end of the intervention, and at six-week and four-month follow-ups. Blood drawn from subjects who wrote about traumatic events was more responsive to PHA (but not Con A). There were no relations between disclosure and alcohol intake, caffeine intake, or exercise over the course of the study. In addition, subjects revealing traumatic events made fewer visits to the health center in the six weeks following the intervention than did members of the control group. Unfortunately, the data do not support an immune pathway because the lymphocyte proliferation data were *not* correlated with health-center visits. This absence of correlation also suggests that increases in health center visits may be driven by psychological influences on decision processes rather than by influences on actual illness (Cohen & Williamson 1991).

Research on how social-support interventions affect immune system function in stressed samples is in its infancy. Existing studies provide only suggestive evidence. Three visits a week for a month by college students to geriatric-home residents resulted in no detectable effects on residents' cellular immune response (Kiecolt-Glaser et al 1985); nor did an intervention (of unspecified

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provided, the nature of the population, the source of the support, strategies for structuring group interaction, and the duration of the intervention.

Personality

The study of the role of personality in health has a long history (Friedman 1990). However, relations between personality characteristics and immunity have received little attention. Personality characteristics correlated with measures of immune status include power motivation (e.g. Jemmott et al 1983, 1990), pessimistic style (Kamen-Siegel et al 1991), and repression (Esterling et al 1993). We limit our discussion to repression/denial because it has been studied in relation both to immune function and to immune system–mediated disease [acquired immunodeficiency syndrome (AIDS) and cancer].

Repression/denial represents a coping strategy against threatening information and is characterized by denial or minimization of distress and negative emotions. Repressors react to stressful stimuli with higher autonomic arousal than persons reporting high anxiety or distress (Weinberger et al 1979).

Esterling et al (1993) found no association of repression with herpesvirus antibodies when repression was operationalized in terms of a low score in trait anxiety and a high score in defensiveness. However, higher scores on a personality inventory assessing repression were associated with the suppression of cellular immune function as indicated by higher levels of herpesvirus antibody in two independent samples (Esterling et al 1990, 1994a). These relations held even after controlling for medication use and a range of health practices. In contrast, Antoni et al (1990) found that gay males who were about to be tested for HIV status who scored higher on a denial coping scale had a *greater* proliferative response to PHA. This work suggests the possibility of a link between repression/denial and cellular immune response but also suggests that the scale used to measure repression/denial is important.

DO PSYCHOLOGICAL FACTORS INFLUENCE IMMUNE SYSTEM–MEDIATED DISEASE?

Invasion of the body by a disease-causing agent is not sufficient cause for disease. Disease occurs when host defenses are compromised or unable to recognize the foreign material. This is why psychological variables that influence immunity have the potential to influence the onset and progression of immune system–mediated diseases. What is less clear is whether psychologically induced changes in immunity are of the magnitude or type that would alter the ability of the body to fight disease (Cohen & Williamson 1991, Laudenslager 1987, O'Leary 1990). Below, we review a selection of studies that addresses the role of psychological factors in the onset and progression of infectious diseases, autoimmune diseases, and cancer. We limit ourselves pri-

marily to prospective or intervention studies and to studies in which disease outcomes are biologically verified or physician documented.

Infectious Disease

UPPER RESPIRATORY INFECTIONS (URI) Early prospective work by Meyer & Haggerty (1962) indicated that both disruptive daily events and chronic family stress were associated with greater risk for upper respiratory infections. Similar results were reported by Graham et al (1986). Measures of life stress were collected from members of 94 families before and during a six-month period in which diary

stress and negative affect. In another study, Stone et al (1992) replicated the relation between stressful life events and susceptibility to URI and identified the same biological pathway as in the work of Cohen et al (1993). Finally, in a

In sum, herpes studies generally support a relation between negative emotional states and disease recurrence. However, the evidence is not entirely consistent, and methodological limitations warrant cautious interpretation of these results. Moreover, existing work does not establish the extent to which such effects are mediated through immune or behavioral pathways.

AIDS Not all persons exposed to the HIV virus become infected. After exposure, both the number of years to manifestation of clinical symptoms and

ported more

in helping the patient to increase his/her functioning. In the education group, patients received emotional support from family during sessions and were encouraged to discuss illness-related problems between sessions with their family members. Regardless of whether family support was available, RA patients in the cognitive-behavioral interventions showed improvement in joint exam, reduced swelling severity, and fewer swollen joints two months after the intervention, compared with the other two groups.

At this point it is unclear why some interventions with RA patients resulted in improved health and others did not, although possible reasons include differences in patient adherence to the interventions' requirements; differing amounts of practice to maintain gains; or differences in such patient characteristics as severity of disease, amount of disability, and sex (Young 1992). Moreover, none of the existing work directly addresses how (i.e whether by means of immune changes, behavioral changes, etc) psychological factors alter disease progression.

Cancer

Cancer comprises a large and heterogeneous group of diseases characterized by the uncontrolled proliferation of cells. Because the immune system is thought to play important roles in tumor surveillance and in preventing the progression and metastatic spread of tumors, psychological factors associated with immunity are considered potential contributors to cancer onset and progression (Anderson et al 1994). The immune function emphasized as a link between psychological factors and cancer is NK activity. The presumed im-

longer lives than patients with stoic acceptance (fatalism) or helpless responses (Greer 1991). Partial replications of this work have been reported (Dean & Surtees 1989, DiClemente & Temoshok 1985). Greer (1991) cautions

attempts to replicate and extend this work will help us evaluate their validity as well as identify behavioral and immune mechanisms responsible for reported outcomes.

CONCLUSIONS

The literature discussed in this chapter is in many ways impressive. First, it provides psychologically and biologically plausible explanations for how psychological factors might influence immunity and immune system–mediated disease. Second, it provides substantial evidence that psychological factors can influence both cellular and humoral indicators of immune status and function. Third, at least in the case of the less serious infectious diseases (colds, influenza, herpes), it includes consistent and convincing evidence of links between stress and disease onset and progression. Although still early in its development, research on autoimmune diseases (at least on RA) also suggests the potential role of psychological factors. Evidence for effects of psychological factors on AIDS and cancer is less consistent and inconclusive. This may be because of methodological limitations inherent in studying these complex illnesses, or it may be because psychological influences on immunity are just not of the magnitude or type necessary to alter the body's response in these cases. Further development and evaluation of psychosocial interventions may be the best approach for providing evidence that allows clear causal inference and at the same time has clinical implications. What is missing in this literature, however, is strong evidence that the associations between psychological factors and disease that do exist are attributable to immune changes. Many of the relations reported in this chapter may be attributable to psychologically induced changes in health behaviors (e.g. health practices such as smoking and alcohol consumption, or degree of adherence to medical regimens); better measurement and control of these variables are essential. Moreover, the inclusion in future studies of immune measures based on the role of the immune system in the specific disease under study may help provide evidence for a direct link among psychological factors, immunity, and disease.

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