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HEALTH PSYCHOLOGY: Psychological Factors and Physical Disease from the Perspective of Human Psychoneuroimmunology

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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 stress, negative affect, clinical depression, social support, and repression/denial 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 considers consistent and convincing evidence of links between stress and negative affect and disease onset and progression. Although still early in its development, research also suggests a role of psychological factors in autoimmune diseases. Evidence for effects of stress, depression, and repression/denial on onset and progression of AIDS and cancer is less consistent and inconclusive, possibly owing to methodological limitations inherent in studying these complex illnesses, or because psychological influences on immunity are not of the magnitude or type necessary to alter the body's response in these cases. 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.

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INTRODUCTION

Much of psychoneuroimmunology's popularity with both the public and the psychological community derives from its promise to explore and explain the common belief that our personalities and emotions influence our health. Can depression, anxiety, psychological distress, social support, or an optimistic view alter our ability to resist infection, autoimmune diseases, or cancer? What are the biological pathways through which psychological characteristics and states yield physical changes? Can we alter immunity and hence disease susceptibility through psychological intervention? Several hundred studies published in the past decade address the relation of psychological characteristics and states to immune function and to health outcomes thought to be determined by immune alterations. In this chapter we highlight what we have learned about the importance of immunity as a link between the mind and the body.

WHAT IS PSYCHONEUROIMMUNOLOGY?

Psychoneuroimmunology (PNI) is the study of the interrelations between the central nervous system and the immune system. The term interrelations is used because the assumption is that the relations are bidirectional. Work with animals has advanced our understanding of this bidirectionality and has provided evidence for nerves connecting the central nervous system (CNS) and the immune system (e.g. Felten et al 1985), for neuroendocrine-induced alterations of specific immune functions (e.g. Shavit et al 1984), and for the exist-

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. Examples of overlap in focus include studies of classical conditioning of human immune response (e.g. Bovbjerg et al 1990, Buske-Kirschbaum et al 1992) and demonstrations of immune-system effects on the CNS as reflected in human performance (Smith et al 1988). The most obvious difference, however, is that the human literature is primarily concerned with behavior and psychological traits and states as drivers of CNS and immune response. The major foci of human studies include establishing whether there is an association between psychological traits and states and immunity, what the biological and behavioral pathways are that are responsible for such relations, and whether psychologically induced changes in immunity are responsible for changes in susceptibility to immune system–mediated disease.

WHAT IS IMMUNE FUNCTION?

The Immune System

The immune system protects the body from damage by invading microorganisms—bacteria, viruses, fungi, and parasites. These foreign materials are called antigens. Most immune system cells are located in the bone marrow, thymus, lymph nodes, spleen, tonsils, appendix, and Peyer's patches (clumps of immune tissue in the small intestines). Because there is no easy way to access the cells of these organs, PNI work with humans is primarily limited to the study of immune processes occurring in circulating peripheral blood. Circulating blood transports immune components between organs of the immune system and sites of inflammation. Components of the immune system that circulate in blood (e.g. some types of white blood cells and antibody) survey for and combat against invading antigens. Therefore, peripheral blood plays a key role in inflammatory and immune processes.

Tests of Immune Function

In this section, we describe the immune system tests most commonly used in human PNI research. Most of the tests evaluate the role of immune cells in peripheral blood.

ENUMERATIVE TESTS The enumerative assay most often used involves simply counting the numbers or percentages of different kinds of white blood cells in the peripheral blood. The white blood cells relevant to this chapter are neutrophils, monocytes, and lymphocytes, including natural killer (NK), T, and B lymphocytes. Quantifying the number of circulating cells is important both because the body cannot respond adequately to antigenic response without a minimum number of each type of immune cell and because an optimal response requires a balance of the various cell types. Both increases and decreases in numbers of circulating cells suggest alterations in the immune system. However, the changes found in the PNI literature are usually quite small, and whether these changes indicate compromised immune function is theoretically unclear.

FUNCTIONAL TESTS Immune response can be divided into cellular *immunity*, in which immune cells directly combat antigens, and *humoral* immunity, in which products of immune cells (e.g. antibody) combat antigens. Although the cellular and humoral subsystems work together in many instances, the functional tests we describe primarily explore the integrity of one or the other.

Lymphocytes are the key cells controlling the immune response. The ability of these cells to proliferate rapidly in the face of an antigenic challenge is essential to an adequate response. Lymphocyte proliferation is a test of cellular immunity that examines how effectively stimulated lymphocytes divide. Lymphocytes are stimulated through incubation with substances (mitogens) capable of nonspecifically inducing T or B lymphocytes to divide. It is assumed that greater proliferation indicates more effective cell function. Commonly used mitogens include phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM).

NK cells may be thought of as serving a surveillance function; they can detect and kill damaged or altered (e.g. infected or cancerous) cells. The NK cell cytotoxic activity assay, another test of cellular immunity, is used to determine how effectively NK cells kill transformed cells. In this assay, immune cells are incubated with tumor cells and tumor-cell killing is measured.

The functional tests described up to this point are in vitro tests; cells are removed from the body and their function is studied in the laboratory. Three in vivo tests that assess the function of cells in the living organism are also used in this literature. One, the quantification of antibodies (Ab) to herpesviruses, is used to *indirectly* assess cellular immune competence (e.g. Glaser & Gottlieb Stematsky 1982). Almost everyone has been exposed to the common herpesviruses. These viruses differ from most other known viruses in that after exposure, they are present in the body all of the time, although often in latent states. When the immune system is suppressed, latent virus replicates. Antibodies are protein molecules produced by the immune system that have the

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 relations between psychological factors and the onset and progression of immune system–mediated disease. The review is limited to studies of the psychological factors that have received the most attention, including stressful life events, clinical depression, negative affect, social support, and repression/denial.

HOW COULD PSYCHOLOGICAL FACTORS INFLUENCE IMMUNITY AND DISEASE?

Figure 1 presents a simplified view of how psychological factors might alter immunity and disease susceptibility. As discussed above, psychological variables may influence immunity through direct innervation of the CNS and immune systems or through hormonal pathways. Behavioral changes that are associated with personality characteristics or that occur as adaptations or coping responses in the face of stressful events or negative emotional states may

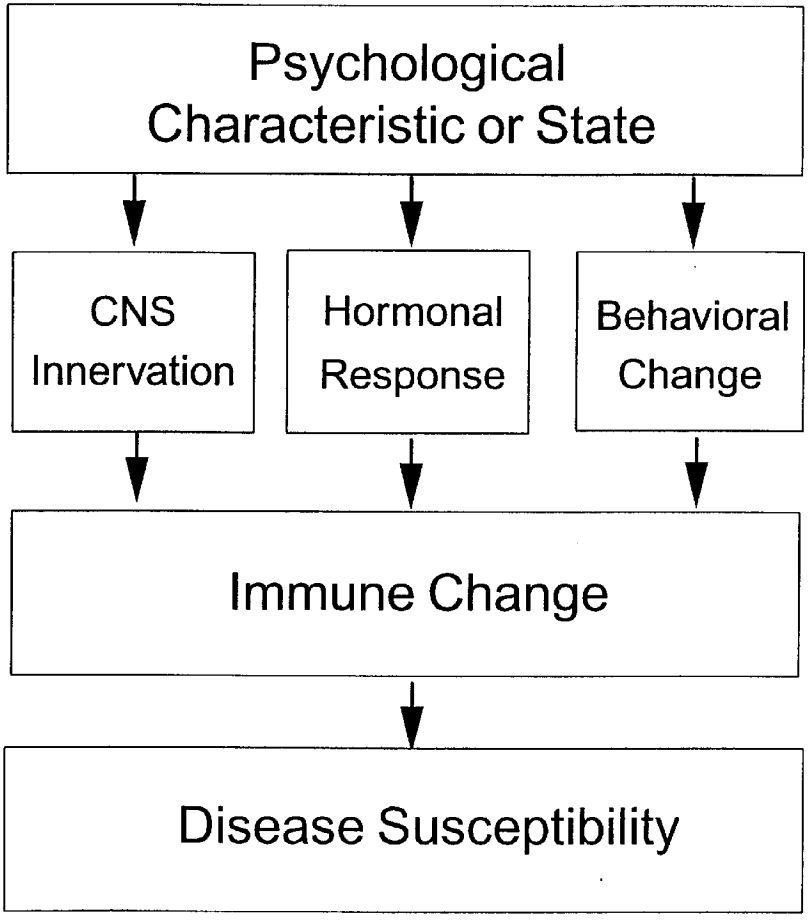

Figure 1 Pathways through which psychological factors might influence onset and progression of immune system–mediated disease. For simplicity, arrows are drawn in only one direction, from psychological characteristics to disease. No lack of alternative paths is implied.

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).

DO PSYCHOLOGICAL FACTORS INFLUENCE IMMUNITY AND DISEASE?

Stress

Stressful life events are commonly believed to alter immunity and hence susceptibility to immune system–mediated disease. When demands imposed by events exceed individuals' abilities to cope, a psychological stress response composed of negative cognitive and emotional states is elicited. It is these responses that are thought to influence immune function through their effects on behavioral coping and neuroendocrine response.

NATURALISTIC STRESSORS In a series of studies, Glaser, Kiecolt-Glaser, and colleagues investigated the impact of medical school examinations on medical students' cellular immune function. In the typical study, students' psychological stress levels and immune responses were assessed during a low-stress baseline period (e.g. just following vacation) and again during a series of important exams. Students reported more stress during exams and showed a decrease in the function of a range of indicators of cellular immune response, including decreased NK activity (Kiecolt-Glaser et al 1984, Glaser et al 1986), lymphocyte proliferation (Glaser et al 1985b, 1987, 1993), lymphocyte production of the chemical messenger gamma interferon (Glaser et al 1986, 1987), as well as an increase in production of antibody to herpesviruses (Glaser et al 1985a, 1987, 1991).

In a study of the role of positive (e.g. accomplishing a goal, experiencing a good interaction with their bosses) and negative (e.g. losing keys, having arguments) daily events in humoral immunity, Stone et al (1994) had community volunteers ingest a capsule containing an innocuous novel protein daily for 12 weeks. The protein acted as an antigen to which the immune system responded by producing antibody. To evaluate the role of daily events in antibody production, volunteers also completed daily diaries and gave daily saliva samples that were used to assess amounts of secretory Immunoglobulin A (sIgA) antibody produced in response to the novel antigen. The reporting of more desirable events was concurrently related to greater sIgA antibody production, and the reporting of more undesirable events was related to less. Desirable events were also associated with increases in sIgA production over two subsequent days. These data provide evidence for the role of day-to-day

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 area surrounding the Three Mile Island (TMI) nuclear power plant. TMI was the site of a serious accident in 1979, and the distress among area residents has remained high (Baum et al 1985). Recently, almost 10 years after the accident, McKinnon et al (1989) found more antibody to herpesviruses in TMI residents than in demographically matched control-group residents, suggesting lower cellular immune competence in the former.

Studies on the impact of the chronic stress associated with caregiving for relatives with Alzheimer's disease (AD) report mixed results. Kiecolt-Glaser et al (1987b) found that caregiving was associated with distress and elevated levels of herpesvirus antibody. The caregivers did not differ from the low-stress control group, however, in a variety of health behaviors thought to affect cellular immunity. In contrast, in a similar study, Irwin et al (1991) found no difference in NK activity between caregivers and controls. Finally, Esterling et al (1994b) compared AD caregivers, former AD caregivers (i.e. those whose AD relative had died at least two years previously), and controls. Former and current caregivers did not differ from each other and had poorer NK-cell response to stimulatory chemicals than the control group. These data suggest that psychological and immunological consequences of chronic stressors may persist beyond the cessation of the actual stressor.

If stress is reliably associated with immune change, can stress-reduction interventions prevent that change? The few existing studies are less than convincing in that regard. However, only one actually addressed the effectiveness of an intervention in the face of a common stressful event. In this study, medical students were trained in relaxation techniques just prior to first-year

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.

ACUTE STRESSORS IN THE LABORATORY Several studies have assessed the effects of acute (i.e. lasting 5–20 minutes) psychological stressors (e.g. speech task, Stroop color word interference task, mental arithmetic) on immune response. The most consistent immune changes following stressor exposure include increased NK and suppressor/cytotoxic T cell numbers and decreased proliferative responses to mitogens, particularly PHA (e.g. Herbert et al 1994, Manuck et al 1991, Naliboff et al 1991, Zakowski et al 1992). One study has shown that immune changes in both cell numbers and function can be found as soon as five minutes after the onset of the stressor (Herbert et al 1994). Most immune parameters return to a resting level by one hour following the cessation of the stressor (Kiecolt-Glaser et al 1992), although some evidence indicates that NK activity remains depressed for as long as 48 hours (Sieber et al 1992). Moreover, stress-elicited immune responses found in the laboratory are at least partly attributable to a dispositional style of responding to stress. This is suggested by data indicating that stress-induced immune responses are reliable across time and tasks (Marsland et al 1995). The existence of dispositional immune reactive styles allows the possibility that greater immune reactivity may place people at risk for stress-elicited immune related disease (Boyce et al 1995, Cohen & Manuck 1995).

Laboratory studies are ideal for exploring biologic mechanisms linking psychological stress to immune change. For example, Manuck et al (1991) concluded that individuals characterized by high sympathetic nervous system (SNS) activation (i.e. large increases in blood pressure, heart rate, and SNS hormones epinephrine and norepinephrine) in the face of acute stressors also showed the largest immune changes. Those demonstrating little or no sympathetic reactivity showed little or no change. This result has been replicated several times (Bachen et al 1995, Herbert et al 1994, Zakowski et al 1992).

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 exposed. However, these studies also include a second factor. Subjects are administered either placebos or pharmacological agents that prevent hormones produced by the SNS from binding to and therefore interacting with immune cells (adrenergic blockers). If the effects of stress on cellular immune function are mediated by the SNS, the pharmacological agents should effectively eliminate stress-induced change in the immune system. In one study, Bachen et al (1995) demonstrated that administering the adrenergic blocker labetalol prevented stress-induced increases in NK-cell number and NK activity and decreases in lymphocyte proliferation in response to mitogen. Benschop et al (1994) have also shown that the adrenergic blocker propranolol prevents the stress-induced increase in NK-cell number and NK activity. Both studies therefore suggest that these immune changes are caused by sympathetic activation following stressor exposure. The interpretation that the SNS is the primary mediator of these effects is also supported by studies that investigate stress-induced immune changes in the context of other key hormonal systems involved in immune regulation. For example, studies have failed to implicate either cortisol (Manuck et al 1991; Zakowski et al 1992, 1994) or opioids (Naliboff et al 1995) in acute stress-induced suppression of either lymphocyte proliferation or NK-cell activity.

Although laboratory stress studies provide valuable information, important questions remain unanswered. For example, to what extent do acute stressor effects found in the laboratory simulate more chronic real-life stressful events, and is laboratory immune reactivity a dispositional marker of susceptibility to stress-elicited disease (Boyce et al 1995, Cohen & Manuck 1995)?

Affect

Research on the role of negative affect in immune response has focused on clinical depression. However, recent work examines relations between different affective states, both negative and positive, and immune response in healthy populations.

DEPRESSIVE DISORDERS Investigation of the immunologic correlates of clinical depression has received considerable attention. A recent meta-analysis of over 40 studies shows that when compared to healthy controls, clinically depressed individuals have lowered proliferative response to PHA, Con A, and

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 dis-

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 et al 1984). Because loneliness is generally associated with psychological distress and negative affect (Peplau & Perlman 1982), these relations might be explicable in the same terms as the effects of negative emotions described above.

There is substantial evidence that poorer marital relations and marital disruption (separation and divorce) are associated with poorer health (Verbrugge 1979). Recent work has searched for potential effects of marital discord on immune function. Kiecolt-Glaser et al (1987a) found that 16 separated and divorced (S/D) women had higher levels of herpes antibody, a lower percentage of NK cells, and lower lymphocyte proliferative response to PHA and Con A than a comparison group of 16 married women. In a similar study, Kiecolt-Glaser et al (1988) found that 32 S/D men reported having more infectious illnesses and had higher levels of herpes antibody than their 32 married counterparts. Finally, a study that categorized newlywed couples on the basis of observed interactions (Kiecolt-Glaser et al 1993) found that those who exhibited more negative or hostile behaviors showed greater decreases over 24 hours in NK activity and proliferative response to PHA and Con A.

Perceived availability of social support has also been associated with immune function. A study of 256 elderly adults (Thomas et al 1985) found that blood samples from persons reporting they had confiding relationships proliferated more in response to PHA than samples from those without confiding relationships. Moreover, this relation was unchanged by controlling for psychological distress and health practices. Similar results were found in a study of 23 spouses of patients with cancer (Baron et al 1990). Six different provisions of social support (including emotional and instrumental forms of support) were associated with higher NK activity and better proliferative response to PHA (but not to Con A). Better immune response among supported persons could not be explained by greater depression or more numerous stressful life events among those with less social support. Glaser et al (1992) found that medical students reporting more available social support produced more antibody in response to a hepatitis B vaccination than those reporting less support, but two studies of HIV-positive men were less successful in establishing relations between social support and immunity (Goodkin et al 1992, Perry et al 1992). However, HIV infection compromises the immune system to a degree

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 length) that provided emotional support and information about finding new jobs modify the decrease in lymphocyte proliferation to PHA suffered by a group of Swedish women who were unemployed for over nine months (Arnetz et al 1987). However, a six-session group intervention with melanoma patients was associated with decreased psychological distress and increased NK activity six months after the intervention (Fawzy et al 1993). This intervention was run by professional facilitators and included such elements as stress management training and education about cancer. How to design appropriate and effective social support interventions is a controversial and as yet unresolved question. Appropriate design depends on definitions of social resources to be

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 data on subjects' respiratory symptoms were collected daily. Illness episodes were validated by nose and throat cultures. Although high- and low-stress groups were almost identical with respect to demographics and health practices, the high-stress groups experienced more verified episodes of illness and more days with symptoms of respiratory illness.

In a study of susceptibility to influenza (Clover et al 1989), 246 individuals in 58 families completed instruments assessing family relationships and individual stressful life events prior to the start of flu season. Stressed ("rigid and chaotic") families showed greater incidence of disease than nonstressed ("balanced") families. However, illness was not related to individual stressful life events.

Increased incidence of URI under stress in these studies may be attributable to stress-induced increases in exposure to infectious agents rather than to stress-induced immunosuppression. For example, persons under stress often seek out others, which increases the probability of exposure. A series of studies using a procedure through which volunteers are intentionally exposed to a virus (viral-challenge trials) provides control for exposure. In these prospective designs, psychological factors are assessed before volunteers are intentionally exposed to an upper respiratory virus. Whether or not persons develop biologically verified clinical illness over the course of 7 to 10 days of quarantine is then assessed as the dependent variable.

Three recent viral-challenge trials suggest interesting relations between psychological stress and URI susceptibility. In a study of 394 volunteers (Cohen et al 1991, 1993), measures of stressful life events, perceived stress, and negative affect all predicted the probability of developing a cold, with greater stress linearly related to greater probability. The relations that Cohen et al reported were found consistently across five different URI viruses. Moreover, these results could not be explained by stress-elicited differences in health practices such as smoking and alcohol consumption or in the numbers of various white blood cell populations or total (nonspecific) antibody levels. It is interesting to note that stressful life events predicted susceptibility independently of (and through a different biological mechanism than) perceived

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 viral-challenge study examining predictors of disease severity (rather than episode onset), Cohen et al (1995a) found that state (but not trait) negative affect measured just prior to viral exposure was associated with more severe colds and influenza as measured by the amount of mucus produced over the course of the illness.

In sum, both stressful life events and psychological stress (perceptions and negative affect) are associated with increased susceptibility to upper respiratory infections. These effects are not generally explicable in terms of stress-elicited changes in health behaviors. However, neither is there any direct evidence yet that increased susceptibility is attributable to stress-induced immunosuppression.

HERPESVIRUS INFECTIONS Herpesviruses are thought to be responsible for cold sores, genital lesions, infectious mononucleosis, and mononucleosis syndrome and deafness in neonates (Kiecolt-Glaser & Glaser 1987). Herpesviruses differ from most other known viruses in that after exposure, they are present in individuals all the time, although often in latent states. The cellular immune response plays a key role both in protection from initial herpesvirus infection and in keeping latent herpesviruses from becoming active (Glaser & Gotlieb-Stematsky 1982). As discussed earlier, one explanation for the increase in herpesvirus antibodies often associated with stressful conditions is that stress suppresses cellular immune function, which allows the latent virus to become active. Is stress associated with a recurrence of clinical disease (lesions) after a period of herpesvirus latency?

In a series of studies of student nurses conducted in the 1970s, negative moods at the beginning of the school year were generally associated with greater numbers of subsequent episodes of verified oral herpes (Friedmann et al 1977, Katcher et al 1973, Luborsky et al 1976). Similar evidence for stress-induced recurrence is provided by both retrospective (e.g. Kemeny et al 1989) and prospective studies of genital herpes (Goldmeier & Johnson 1982, McLarnon & Kaloupek 1988; see critiques in Cohen & Williamson 1991). A recent study of 125 college students provides an elegant test of the role of stress in herpes recurrence through an examination of several specific causal models (Hoon et al 1991). This work indicates that stress increases vulnerability to illness in general (nonherpes) and that it is this increase in nonspecific vulnerability that results in herpes recurrence. Hoon et al did not address the physiological basis for this vulnerability, but because the illness vulnerability measure was heavily influenced by highly prevalent infectious diseases (colds and influenza), an immune basis is plausible.

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 the severity of illness at all stages of AIDS vary tremendously. Poor nutrition, drug use, repeated HIV exposure, and other concurrent viral infections can all accelerate HIV disease progression. However, even after these factors are accounted for, a good deal of variability in response to the virus is unexplained. Psychological variables are thought to contribute to host resistance to the HIV virus by altering relevant behavioral practices and hormonal and immune environments (Baum & Nesselhof 1988, Kemeny 1994, Schneiderman et al 1994).

Studies of the roles of stress and negative affect in the progression of HIV infection are inconsistent in their conclusions. Burack et al (1993) found that HIV-positive gay men who were depressed at baseline showed greater declines than a nondpressed control group in numbers of T-helper cells (an important prognostic indicator of HIV) over a subsequent period of five years. However, depression was not associated with either the onset of AIDS or mortality. In contrast, in another study of HIV-positive gay men, Lyketsos et al (1993) found no association between depression and changes in T-helper cell counts, AIDS onset, or mortality over a subsequent period of eight years. In a recent study (Kemeny et al 1995), HIV-positive men who recently lost an intimate partner to AIDS showed an increase in levels of an immune marker of disease progression (serum neopterin) as well as a decrease in lymphocyte proliferation in response to PHA. Neither immune change was explicable in terms of use of recreational drugs, alcohol, or smoking. Finally, Kessler et al (1991) did not find correlations between recent losses or stressful life events during the six months prior to baseline and two disease outcomes—T-helper cell count and onset of symptoms associated with AIDS over the subsequent two to three years. All of these studies can be faulted for focusing on baseline stress and depression as predictors of the long-term course of disease. These variables are not stable over time and there is a need to examine triggers closer to the time of disease onset (Cohen et al 1995b).

Investigations of the role of denial in AIDS are inconsistent. Ironson et al (1994) studied disease progression in initially asymptomatic HIV-positive men involved in a behavioral intervention program. Persons who denied their diagnosis did poorly on markers of disease progression one year later (poorer PHA-stimulated proliferation and greater decline in T-helper cells) and re-

ported more symptoms two years later. Immune function at one year was associated with symptoms at a two-year follow-up, but no direct test of immune mediation of the association between denial and symptoms was conducted. In contrast, Reed et al (1994) reported that HIV-positive gay men who refuse to accept their disease and its implications live nine months longer than those who realistically accept them.

Finally, in a single study of social support (Theorell et al 1995), 48 hemophiliac patients who were infected with the HIV virus were followed for five years. Those who reported less access to emotional support at baseline showed a greater decline in T-helper cells over the course of the study than those with stronger support systems. There were no differences between groups in number of symptoms of AIDS or in rates of mortality.

INTERVENTIONS Two studies investigated the potential impact of stress management interventions on immune markers of AIDS progression. A study of men diagnosed with HIV infection (Coates et al 1989) found no differences in T-helper cell numbers or lymphocyte proliferation between treated and untreated patients. In a study of individuals' responses to being diagnosed HIV positive (Antoni et al 1991), those who received stress management prior to notification responded with a better immune status (greater T-helper and NK cell numbers and greater PHA-stimulated lymphocyte proliferation) than no-treatment controls. Both of these studies had small sample sizes and short follow-ups, and neither preselected participants for particular vulnerabilities (e.g. depression). Intervention work is of great theoretical and practical importance and further studies using various proven approaches as well as improved methodologies should be the highest priority.

Evidence reported above is at best mixed in its support for a role of psychological variables in the progression of HIV infections. Investigations of the role of psychological factors in AIDS, however, pose difficult methodological challenges. Time since infection is usually indeterminable; there is difficulty in controlling for effects of medication; and the work published to date has lacked sufficient time-lines for assessing mortality. Further work attending to the stability of the psychological predictors, recognizing that psychological factors may have different influences on different stages of disease, and assessing alternative explanations for relations would be welcome.

Autoimmune Diseases

In autoimmune disease, the body begins to attack its own cells and organs. The immune system produces antibodies that attack its own tissues (autoantibodies), and T lymphocytes fail to discriminate self from nonself and attack normal body tissue (Rabin et al 1989). Autoimmune disorders include rheumatoid arthritis (RA), insulin-dependent diabetes, lupus, Graves disease, inflam-

matory bowel disease, and multiple sclerosis. Each is associated with different organs and with somewhat differing immune processes. Most of the work on the role of psychological factors in autoimmune disease has involved patients with RA. The primary symptom of RA is inflammation of the joints, and progression of the disease leads to erosion of cartilage and finally to joint-cavity destruction.

Numerous clinical observations and several retrospective studies suggest that psychological factors, including stressful life events (Homo-Delarche et al 1991, Rimón et al 1977) and less-supportive atmospheres (DeVellis et al 1986, Moos & Solomon 1964), play a role in the onset and exacerbation of autoimmune diseases. More impressive are studies evaluating the effectiveness of cognitive-behavioral interventions on RA progression (review in Young 1992). Although not all interventions are successful in affecting disease outcomes (e.g. Parker et al 1988, Strauss et al 1986), many have been. For example, Bradley et al (1987) assigned RA patients to one of three groups. The first was a cognitive-behavioral program consisting of biofeedback training, RA education, relaxation training, behavioral goal setting, and use of self-rewards. The second included a social support condition consisting of small group meetings with family members or friends to discuss RA education, current coping strategies, and the development of improved coping methods. The third group was a no-treatment control. Compared with the other two groups, the patients assigned to the cognitive-behavioral program showed greater reductions in pain intensity, inflammation, and serum levels of rheumatoid factor (a marker of disease progression) immediately posttreatment. However, these benefits were no longer evident six months later. O'Leary et al (1988) also used a cognitive-behavioral intervention and compared disease outcomes of patients undergoing the intervention with patients assigned to a control group that received only printed information (i.e. a bibliotherapy control). The treatment group met once each week for two hours over a five-week period, and assessments of disease outcome were made immediately before and after the five weeks of intervention. When compared with the control group, patients receiving the cognitive-behavioral intervention reported reduced pain, and rheumatologists who were blind to patient group assignment found improved joint conditions among these patients.

Finally, Radojevic et al (1992) conducted a six-week-long intervention and assigned RA patients to one of four groups: cognitive-behavioral intervention with family support, cognitive-behavioral intervention alone, education with family support, or a no-treatment control group. The family support component of the intervention differed depending on the condition, although in both groups family members attended the meetings. In the cognitive-behavioral intervention, family support consisted of learning how RA affects the family environment and how the family can assist the patient in coping with pain and

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 importance of NK activity is based on the combination of reliable findings associating psychologic variables with NK activity (Herbert & Cohen 1993a,b) and on the association of depressed NK activity and increased metastases in animal models (Gorelik & Herberman 1986). However, different cancers are very different diseases, and immune and psychological factors may play a role in some but not in others (Holland 1990, Rabin et al 1989). Similarly, psychological and immune processes may vary at different phases of tumor growth—tumor induction, growth, and metastases (Sklar & Anisman 1981).

We reviewed work suggesting that both depressed affect and clinical depression have been associated with changes in immune function (including lower NK activity). Depression has also received considerable attention as a contributor to cancer; however, the results are not entirely consistent. This work includes prospective epidemiological studies of initially healthy persons that predict subsequent cancer incidence and mortality as well as studies that predict survival among diagnosed cancer patients.

Evidence from prospective incidence and mortality studies is mixed. In a 20-year follow-up of 2020 men who completed the Minnesota Multiphasic Personality Inventory in 1957–1958, those with higher depression scores had twice the risk of dying of cancer 17 (Shekelle et al 1981) and 20 years (Persky et al 1987) later than did their less depressed counterparts. These effects were nonspecific to site or type of cancer and could not be explained by differences in health practices. It is interesting to note that when a formula was used to calculate whether patients were "clinically depressed" from the self-reported scale, no relation to cancer was found (Bieliauskas & Garron 1982). Grossarth-Maticek et al (1983, 1985) found that persons with long-lasting hopelessness and depression were more likely than those neither hopeless nor depressed to develop cancer over a 10-year follow-up. This relation was independent of a series of biological predictors of disease onset. Several 10- to 20-year prospective studies have failed to find that clinical depression as assessed by self-report depression scales placed people at risk for either cancer incidence or cancer mortality (Hahn & Petitti 1988, Kaplan & Reynolds 1988, Zonderman et al 1989). Depression has, however, been associated with markers of disease progression (Levy et al 1985) and shorter survival among patients diagnosed with cancer (e.g. Derogatis et al 1979, Weisman & Worden 1975).

Why are existing data inconsistent? Work on the role of depression in cancer incidence and mortality has focused on undifferentiated cancer outcomes, and greater emphasis on specific disease types and sites may be necessary to clarify this literature. The temporal instability of both depressive affect and clinical depression and the possible role of more acute depressive episodes in cancer onset and progression also need to be recognized (Cohen et al 1995b). This requires repeated measures of depression over the course of longitudinal studies as well as testing at shorter intervals between depression and disease onset.

Evidence discussed above addressed the role of interpersonal relationships and support in immunity. Among cancer patients, greater access to social support has been associated with better prognostic indicators (Levy et al 1985) and longer survival (Funch & Marshall 1983, Weisman & Worden 1975). However, the effects of social support on survival may occur for younger but not for older women (Funch & Marshall 1983), and both disease onset and mortality may be associated with social isolation among women but not men (Reynolds & Kaplan 1990). This work is consistent with other research on the role of social support and suggests that different social structures and resources may have different implications for different populations, particularly as defined by gender and age.

Finally, a 15-year study suggests that patients who respond to nonmetastatic breast cancer with a fighting spirit or with denial have less recurrence and

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 that these results have been found in the context of breast and cervical cancer and that generalizations to other cancers are not warranted.

Although there are many consistencies in these correlational literatures, as a whole they must be viewed in light of several concerns and qualifications. The problems associated with cancer (e.g. undetected premorbid states, difficulty in quantifying severity at any stage, differences in biology of different tumors, difficulty in assessing and controlling for medication and compliance with medical regimens) make it difficult (and often impossible) to design studies that eliminate important alternative explanations. Correlations may be spurious—i.e. derived from other variables such as toxic workplaces, viruses, or chronic infections that influence both psychological characteristics and cancer (Sklar & Anisman 1981). Moreover, although psychological variables may affect survival, the contribution is relatively small and is overshadowed by biological factors. Hence psychological variables are least likely to play a role in later and more serious stages of disease (e.g. Cassileth et al 1985, Jamison et al 1987).

INTERVENTIONS Two recent intervention studies provide the most provocative and convincing evidence for a role of psychological factors in cancer progression. In one (Fawzy et al 1993), 66 malignant-melanoma patients were randomly assigned to either an intervention or a no-treatment control group. The intervention combined education, stress management, coping skills, and discussion with patients and facilitators and consisted of six 90-minute sessions. Six months after the intervention ended, participants in the intervention group showed reduced psychologic distress, enhanced immune function (increased NK activity), and changes in immune cell counts (decreased T cells, increased lymphocytes) when compared with patients in the control group. The intervention also decreased recurrence and increased survival as assessed six years later. Alterations in immune outcomes, however, did not explain the intervention's effect on mortality. In the other intervention study (Spiegel et al 1989), 58 patients with metastatic breast cancer were randomly assigned to either an intervention or a no-treatment control group. The intervention consisted of weekly 90-minute meetings for one year. The highly structured meeting focused on various problems associated with terminal illness and on ways to improve relationships. Ten years later, there was an 18-month survival advantage associated with the intervention. No immune measures were assessed. These studies are conceptually important because they are experimental demonstrations of the significance of psychological factors, and they are practically important because they suggest a significant role for psychological interventions in cancer survival. Ongoing

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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