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Stress, Emotion, and Human Immune Function

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This article provides a review of empirical evidence linking emotional processes to immune function in humans. Acute stressors have produced mixed effects on immunity, presumably through differential activation of physiological stress systems. Chronic stress has been associated with suppression of immune function, and there is evidence that the immune system may not adapt over time. Effects of stress accompanying social disruption and psychological depression, when demonstrated, have been consistently adverse. Certain personality styles may enhance or degrade immune response. Relationships between psychosocial factors and immunity have been identified for several diseases, including cancer, acquired immune deficiency syndrome, and autoimmune diseases; psychosocial interventions have been tested with variable results. Theoretical and methodological considerations are summarized and directions for future research suggested.

Since ancient times, people have believed that psychological factors, such as emotional experience, personality, and coping style, can affect disease susceptibility and the course of disease (Dubos, 1965; Shukla, Solomon, & Doshi, 1979). With the discovery a century ago of pathogens as causes of infectious disease, the primary focus of biomedical research became the control and elimination of these agents, leading to the important developments of antibiotic medication and inoculation. Recent years, however, have seen a resurgence of interest in the influence of psychosocial factors on immunologically mediated illness, including cancer and autoimmune disorders as well as infectious disease (Coe & Levine, in press; Jemmott & Locke, 1984). Much of this research has provided evidence of direct association between psychological processes and illness. However, the assumption that such effects are mediated by psychological influences on immune function could not be validated until improved methods of measuring immune parameters became available. The astonishing advances made in the field of immunology in recent years have contributed substantially to the success of efforts to elucidate the processes by which psychosocial factors can influence health outcomes.

In this article, I review research in the general area of human psychoneuroimmunology (PNI), beginning with a brief description of the immune system and a discussion of pathways for neuroendocrine mediation. Following these preliminaries, a review of research examining the relationship of emotional processes to both basic immune function and the development and course of several immune-related illnesses is provided. In the latter discussion, I include only those studies that examined directly the immunologic mediation of psychological influences on health.

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The Immune System: An Overview

A comprehensive description of human immune function is well beyond the scope of the present paper. Although the interested reader is referred to a standard text in the area (e.g., Roitt, 1988; Roitt, Brostoff, & Male, 1989; see also Borysenko, 1987), an understanding of basic immune function sufficient for the comprehension of research findings in PNI is not difficult to attain. Moreover, because gaining expertise in all of the fields relevant to PNI is virtually impossible, most PNI investigators adhere to a collaborative model to design, complete, and interpret their research most effectively.

The general function of the immune system is to identify and eliminate foreign, "non-self" materials that contact or enter the body. These foreign materials are called antigens and include bacteria, viruses, parasites, and fungi. Components of the immune system are also capable of identifying and destroying cells that have undergone alterations associated with malignancy and of directing responses against non-self agents, such as donated organs. The immune system is composed of specialized cells that originate in the bone marrow and that mature and are sequestered in particular organs, such as the thymus, the peripheral lymphoid organs, the spleen, and the lymph nodes. From these organs, the specialized cells are released into the blood; they may also return to these organs from the blood. In most human research, cells are collected from the peripheral blood for laboratory analysis.

Types of Immune Cells

Identification of numerous specific types of cells became possible with the development of *monoclonal antibodies,* or molecules that adhere to specific receptors found on the cells. These receptors are identified by the nomenclature *leu* or, more recently, *cluster designation* (CD), followed by the identifying number. Monoclonal antibodies can be tagged (for example, with flourescent markers) so that they can be identified and

counted, by means of a method called flow cytometry. The most important cells in the immune system are the leukocytes (commonly referred to as white blood cells). There are three main categories of leukocytes: granulocytic cells, monocytes/macrophages, and lymphocytes. Granulocytic leukocytes include (a) neutrophils (also called polymorphonuclear leukocytes or PMNs), which are phagocytes (literally, eating cells) that engulf and destroy bacteria in a nonspecific manner; (b) eosinophils, which similarly engulf antigen–antibody complexes (described later) and defend against some parasites; and (c) basophils, which release histamine and other substances to increase vascular permeability during inflammatory responses, thus facilitating migration of other immune cells to the region.

The monocyte/macrophage is a cell that achieves a more specifically targeted phagocytosis. Monocyte is the name given the cell in its less mature form, when it resides in the blood stream. When it enters tissue, the cell is referred to as a macrophage. These cells recognize certain carbohydrates on the surfaces of microorganisms, as well as other molecules (immunoglobulins, described later) that are present during the immune response. In addition to phagocytosis of microorganisms, moncyte/macrophages play other roles, such as "presenting" antigen to lymphocytes.

Lymphocytes, which are for the most part cells designed to attack specific targets, comprise roughly 20% of the circulating leukocyte pool and are predominantly of two types: B and T cells. B cells comprise the humoral arm of the immune response, being responsible for the production and secretion of antibodies, highly specific molecules (immunoglobulins) that recognize and combine with their target antigens. When a B cell encounters its target antigen, it develops into an antibody-producing *plasma* cell and also reproduces and multiplies (proliferates) so that the infection can be managed rapidly. This process is referred to as *clonal expansion* or *blastogenesis.* Ultimately, the antibody–antigen complexes are destroyed by phagocytes. There are five classes of immunoglobulins: IgG, IgA, IgM, IgD, and IgE. Immunoglobulins comprise the predominant response to bacterial infection and provide specific defense against some viruses. IgA, an antibody that has been assessed in PNI research, is present in mucous secretions, such as saliva and nasal and genitourinary secretions. After an initial response to a specific antigen, "memory B cells" are created that produce more rapid and efficient response to repeated exposure; this is the basis for the effectiveness of inoculation.

T cells (so called because they mature in the thymus—B cells are released from the bone marrow, or the bursa in chickens) provide cell-mediated immunity; that is, they make direct or close contact with the antigen, which may be a virally infected or cancerous cell. There are three general types of T cells (although it is possible to identify many more specific types within and between these categories). Cytotoxic T cells are capable of destroying target cells. The other two types function primarily as regulators of the immune response. Helper T cells (T4 cells) enhance the immune response, whereas suppressor T cells reduce it. The CD8 receptor is found both on cytoxic T cells and suppressor T cells. Many readers will recognize that helper T cells are the primary target of the human immunodeficiency virus (HIV), another being the monocyte/macrophage, which probably transports the virus into the brain. Another lymphocyte-like cell, the natural killer or NK cell, destroys virally infected cells and certain types of tumor cells and micrometastases.

Enumeration measures quantify the types of cells described in the preceding paragraphs to assess the efficiency of the immune system. Two measures are generally derived: absolute numbers of cells within a given volume of blood, and percentages of cells constituting each subtype. It is also possible to identify cells that have become activated in response to an antigen. Although lymphocyte numbers have been examined in numerous studies, the significance and interpretation of changes are controversial (Cohen, 1987). It is probable that alterations in cell numbers found in the blood frequently reflect redistribution of cells to (or from) lymphoid organs, rather than cell destruction; inferences regarding consequent disease susceptibility are difficult to draw in studies in which health outcome is not assessed. In addition to the use of enumeration measures, immune function can be assessed in a variety of ways.

Functional Assessment of the Immune System

Perhaps the most basic function of immune cells when they contact antigens is proliferation or blastogenesis. One of the oldest and most common methods to measure lymphocyte blastogenesis involves exposing lymphocytes (separated from the rest of the blood) to relatively nonspecific antigens called *mitogens.* The three most commonly used mitogens are phytohemaglutinin (PHA), concanavalin A (ConA), and pokeweed mitogen (PWM). In these assays, lymphocytes are cultured with the mitogen in a medium to which radioactive thymidine (a protein) has been added. As the cells proliferate, they take up the thymidine, which can be identified in the cells. There is some response specificity, with PHA, ConA, and PWM affecting helper T cells, suppressor and cytotoxic T cells, and B cells, respectively; however, the correspondence is poor and lymphocyte responses to the three mitogens are generally highly correlated. The assay tends to yield variable results, being affected by the reagents and batch of mitogen used.

NK cell function can also be assessed. In this assay, cells are cultured with foreign target cells, which are labeled with chromium. When each target cell is destroyed, or lysed, the chromium is released into the surrounding fluid (supernatant), where it can be measured. NK cell activity has been assessed in many psychoimmunologic studies.

Levels of antibodies in serum or saliva may also be measured. Antibodies directed against specific antigens (which have in some studies been introduced by the experimenters), as well as levels of antibodies within a class, such as IgA, may be measured. Herpes virus antibodies have been assessed in a number of PNI studies. The level of these antibodies is thought to reflect the competence of the T cells in keeping the virus sequestered and latent: As the virus escapes, antibodies against it are produced and released into the bloodstream. Herpesviruses include herpes simplexes 1 and 2 (HSV 1 and HSV 2), which are responsible for cold sores and genital herpes, and Epstein-Barr virus (EBV), which causes mononucleosis upon initial infection (although not in all cases).

Some immune cells secrete soluble factors, called *interleukins*

or *lymphokines* (if the cell is a lymphocyte), which provide communication between different cells within the immune system. This may involve amplification of the target cell's response, as in the cases of T-cell-produced Interleukin (Il)-2 and interferon, or direction of the target cell toward the inducing cell, a process called chemotaxis. Interleukins are produced by cells that have become activated by contact with an antigen. It is thus possible to assess immune function by assaying levels of these soluble factors following lymphocyte stimulation.

The particular immune measures selected for study should, ideally, reflect the specific goals of the investigation. For example, if the subject population is one with a particular disease (e.g., cancer), the immune parameters studied ought to be relevant to the disease outcome (such as NK cell activity). In another example, healthy college students are probably most at risk for upper respiratory infection, so salivary IgA might be a relevant immune measure for that population. The nature of the emotional experience being studied may also guide the choice of immune parameters, as indicated by the following section on neuroendocrine mediation. Researchers' heretofore heavy reliance on mitogen stimulation response is likely to be replaced with the more specific tests of immune function currently in use or being developed.

Neuroendocrine Mediation of Psychoimmunologic Effects

Stress and emotions have been known for some time to be associated with substantial physiological changes, including activation of the sympathetic adrenal–medullary (SAM) system, the hypothalamic–pituitary–adrenocortical (HPAC) system, and other endocrine systems (Asterita, 1985; Cannon & de la Paz, 1911; Frankenhauser, 1983; Henry & Stephens, 1977; Levine & Ursin, 1980; Selye, 1956). The two major stress systems (SAM and HPAC) affect numerous aspects of immunity. In psychological terms, the SAM and HPAC systems have been described as the effort and distress systems, respectively (Frankenhauser, 1983), or as the fight-or-flight and conservation–withdrawal systems (Henry & Stephens, 1977). Although the sympathetic nervous system is engaged most strongly in connection with fear and anger, as well as other acute emotional states such as excitement, activation of the pituitary–adrenocortical system is thought to occur during threats appraised as more overwhelming and less readily coped with (Henry & Stephens, 1977). Activation of the adrenocortical system often accompanies chronic stress, as well as clinical depression (Gibbons, 1964; Gitlin & Gerner, 1986). SAM activation is accompanied by the release of epinephrine, norepinephrine, and other catecholamines into the bloodstream, whereas HPAC activation results in the release of adrenocorticotropic hormone (ACTH) and corticosteroids (cortisol in humans and other primates). This may be an overly simplistic view, however, because both stress systems are often engaged during stressful encounters.

More recently, it has become clear that endogenous opioids, morphine-like peptides that are found in the brain and periphery, are released in response to stress. Opioid activation produces stress-induced analgesia in animals (reviewed in Kelley, 1986) and humans (Bandura, O'Leary, Taylor, Gauthier, & Gossard, 1987). It accompanies pain-induced psychological stress and has recently been demonstrated to be a response to stress even in the absence of pain or physical duress (Bandura, Cioffi, Taylor, & Brouillard, 1988). There are several different opioid peptides, including beta-endorphin, which is released from the pituitary, and methionine (met-) enkephalin, which is released from the adrenal glands.

These neuroendocrine processes are among those that presumably mediate the effects of emotional processes on the immune system (reviewed in Antoni, 1987). In evaluating this literature it is important to note that effects may be demonstrated in three different ways: Hormones (for example, catecholamines or corticosteroids) may be (a) generated endogenously by stress or (b) administered medically (within the organism, or in vivo) or (c) added to the assay (in vitro). The magnitude of effect is likely to be lowest in the first situation, intermediate in the second, and largest in the third, although the direction of influence may be affected by the amount of hormone.

Several mechanisms of sympathetic influence on immune function have been elucidated. One is the release of catecholamines, which when simulated with injections of epinephrine, results in redistribution of lymphocytes out of areas of storage and into circulation while reducing the lymphocytes' functional efficacy (Crary, Borysenko, et al., 1983; Crary, Hauser, et al., 1983; Eriksson & Hedfurs, 1977; Felten, Felten, Carlson, Olschawka, & Livnat, 1985; Gader & Cash, 1975). Direct sympathetic innervation of lymphoid organs has been demonstrated in the mouse (Williams et al., 1981). In addition, injection of norepinephrine has been shown to increase NK cell activity (Locke et al., 1984).

On the other hand, cortisol and pharmacological glucocorticoids seem to be primarily suppressive (reviewed in Cupps & Fauci, 1982; Meuleman & Katz, 1985). Administration of corticosteroids results in reductions of lymphocyte numbers in the bloodstream that are primarily T cell and monocyte specific and due mostly to redistribution of cells (Fauci & Dale, 1975), an exception to this being neutrophils, whose numbers increase following corticosteroid administration (Dale, Fauci, & Wolff, 1974). In general, cortisol seems to have greater suppressive effects on the cellular (T-cell mediated) than the humoral (B-cell mediated) arm of the immune response (Meuleman & Katz, 1985). Impaired Il-2 production by T cells (Gillis, Crabtree, & Smith, 1979) and reduced PHA response (Gordon & Nouri, 1981) have been noted following administration of corticosteroids. There is also evidence for suppressive effects on NK cell activity of cortisol and pharmacologic corticosteroids in vivo (Onsrud & Thorsby, 1981) and in vitro (Gatti et al., 1987).

Evidence for effects of opioids on immune function comes from animal studies showing suppressive effects of electric-shock-induced opioid activation on lymphocyte response to mitogens and NK cell activity (reviewed in Morley, Kay, Solomon, & Plotnikoff, 1987). In addition, people who are addicted to exogenous opiates (e.g., heroin) display reduced lymphocyte response to mitogens, have fewer helper T cells, and display poor phagocytosis by polymorphonuclear cells (also reviewed in Morley et al., 1987). In vitro addition of opioid peptides to immunologic assays has been shown to enhance NK cell activity (Kay, Allen, & Morley, 1984; Mandler, Biddison, Mandler, & Serrate, 1986; Mathews, Froelich, Sibbitt, & Bankhurst, 1983),

and this has led to the use of metenkephalin as a treatment for cancer and acquired immune deficiency syndrome (AIDS; Wybran & Schandene, 1986). In vitro opioids have also been shown to reduce lymphocyte response to PHA (McCain, Lamster, Bozzone, & Grbic, 1982) and to enhance monocyte chemotaxis (Ruff, Wahl, Mergenhagen, & Pert, 1985; Van Epps & Saland, 1984).

In fact, most hormones have been shown both to be stress responsive (Asterita, 1985) and to have immunologic effects (Grossman, 1985; Kaeberle, 1984). A variety of neuropeptides, or proteins that modulate neural activity, have been found to influence immune function (Morley et al., 1987). Interestingly, receptors for most hormones and neurotransmitters have been found on the surfaces of lymphocytes, and these cells themselves secrete neuroendocrine precursor cytokines, providing pathways for bidirectional communication between the neuroendocrine and immune systems (Blalock, 1984, 1989; Camara & Danao, 1989; Hall & O'Grady, 1989; Morley et al., 1987). Interleukins, such as Il-1, have been shown to affect brain activity (Breder, Dinarello, & Saber, 1988) and certain immunologic treatments, such as the infusion of interferon in the treatment of cancer, have been shown to have neurologic effects (Smedley, Katrak, Sikora, & Wheeler, 1984).

Thus, extensive pathways and mechanisms for the influence of psychological processes on immune function have been identified, and no doubt many remain to be identified in the future. It is to be hoped that a comprehensive view of psychoimmunological phenomena will eventually include specification of the associations between specific subjective states, neuroendocrine processes, and immune function.

In the following sections, I review the evidence that currently exists for emotional influence on immune function in humans. In this review, I have not included research demonstrating immunologic effects on the nervous or endocrine systems, investigations utilizing animal models, or research describing associations between emotional processes and illness outcomes in which immune function is not examined.

Psychosocial Factors and Basic Immune Function

A growing body of evidence suggests that psychological stress can alter basic immune processes. Research has been focused on the effects of naturally occurring stressors on immune system functioning in healthy people. Although some researchers believe that substantial fluctuations in immune function can be tolerated without producing increased susceptibility to disease (e.g., Cohen, 1987), there is nevertheless much value in examining relationships between psychosocial factors and immunity in populations free from the immunologic concomitants of any specific disease. Viewed in conjunction with research focusing on specific illnesses, such findings contribute to a fuller understanding of psychoimmunologic processes that may have biological, if not necessarily clinical, significance.

Acute Stressors

In most psychoimmunology studies, the effects of acute, short-term stress on immunity have been examined. By acute stress, I mean the stress associated with a single event, even though the duration of anticipatory or consequent distress may vary. In early research, the immunologic effects of the stress of splashdown during manned spaceflight were examined. In one study, Apollo astronauts displayed higher lymphocyte counts but no change in response to PHA following splashdown (Fischer et al., 1972). Further research with Skylab astronauts revealed an increase in numbers of polymorphonuclear leukocytes, a decrease in percentages of T lymphocytes, and reduced response to PHA after splashdown (Kimzey, 1975; Kimzey, Johnson, Ritzman, & Mengel, 1976). Serum levels of cortisol and catecholamines were elevated during spaceflight and splashdown. These studies are among the few demonstrating elevations in numbers of total lymphocytes and other immune cells. The high level of fear (and associated epinephrine release) associated with this type of stressor may be responsible for this effect, which is similar to that produced by epinephrine injection. Unfortunately, correlations between these neuroendocrine mediators and the immune changes were not reported. It should be noted that research utilizing spaceflight stress may confound psychological and physiological effects of the stressor on immune function.

Another early stress paradigm was sleep deprivation, used by Palmblad and colleagues. In these studies, subjects were kept awake for 48–77 hours. Among the immune changes observed in these studies were reduced phagocytic capacity of leukocytes, increased interferon production (Palmblad et al., 1976), and diminished response of lymphocytes to mitogens (Palmblad, Bjorn, Wasserman, & Akerstedt, 1979). Sleep deprivation studies also should be interpreted with caution because they may confound psychological and physiological effects of the stressor.

The stress of academic examinations has been used in a number of studies. Dorian, Keystone, Garfinkel, and Brown (1982) compared 8 psychiatry residents undergoing an oral fellowship exam with 16 psychiatrists and psychiatry residents not taking an exam. Three experimental subjects reported little distress and 7 control subjects reported high levels of distress; they were eliminated from analysis. Two weeks before the examination, the students being tested had higher B- and T-cell counts, reduced in vitro antibody synthesis, and lower response to mitogens. Surprisingly, cortisol levels were higher in the nonstressed group; catecholamines were not measured.

In a comprehensive series of studies, Kiecolt-Glaser, Glaser, and colleagues investigated a variety of immune changes resulting from examination stress. Medical students underwent immunologic assessment during a lower stress baseline period, when no exams were given and the students were less distressed; they were assessed again a month later, during the examination series. A number of immunologic changes were observed. Antibody titers to HSV-1, EBV, and cytomegalovirus (CMV) were higher at exam time; this was interpreted to indicate poorer control of the latent herpesviruses by the cellular immune response (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985). In a subsequent study, Glaser et al. (1987) demonstrated alterations in leukocyte migration-inhibition factor, a lymphokine whose production is suppressed during recrudescence of HSV 2. Glaser, Kiecolt-Glaser, Stout, et al. (1985) demonstrated reductions in the percentages of helper T cells

and suppressor/cytotoxic T cells, and diminished responses to mitogens. During exams, lytic activity of NK cells was reduced, but plasma levels of IgA increased (Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984). Lymphocyte production of interferon was greatly suppressed as well, from a mean of 2,000 units at baseline to 80 units during exams (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986). Because interferon is a regulator of NK cell growth and activity, it is likely that changes observed in NK cell activity in these studies can be ascribed to reduced interferon production.

A frequent criticism of research employing healthy subjects is that observed alterations in immunity may be of little clinical significance; that is, even large shifts in immune parameters can be endured and corrected without illness in healthy people. Glaser et al. (1987) addressed this issue in a recent study and found an increased incidence at exam time of self-reported illness—primarily upper-respiratory-tract infections—and number of days during which activity was limited by illness. Glaser et al. included three baseline and three exam-time assessments over the course of an academic year; hence, seasonal changes cannot account for the findings. However, self-reports of illness may be influenced by demand characteristics and neuroticism (Watson & Pennebaker, 1989). Furthermore, Glaser et al. did not report correlations between reported illness and immune function which, if significant, would strengthen the proposed linkages between stress, immunity, and health.

Another criticism of psychoimmunologic research in general is that apparent relationships between psychological stress and immune function may be mediated by alterations in diet or sleep patterns secondary to stress, the stress itself being neither a necessary nor a sufficient cause of the immune changes. In much of the research conducted by the Kiecolt-Glaser and Glaser team, the amount of sleep was recorded and nutritional status was determined. The latter was accomplished with assays for serum albumin and transferrin, an iron-transporting protein whose levels are related to dietary iron intake (Kiecolt-Glaser et al., 1986; Glaser et al., 1987). Although numerous nutrients (as well as caffeine and alcohol) have not consistently been assessed, results from these studies generally suggest that changes in sleep and diet do not account for the immune changes occurring in response to this stressor.

A recently developed laboratory paradigm for producing stress-related changes in immunity utilizes the fear experienced by phobics when exposed to the feared object. In this research, subjects experience marked distress while undergoing guided mastery therapy, a highly successful treatment modality. In a recent study (Wiedenfeld et al., 1990), snake phobics were assessed—across a number of immune parameters, heart rate, and salivary cortisol levels—during an initial baseline visit in the first week, a two-day treatment period in the second week, and a posttreatment follow up (when the snake was handled with full confidence) in the third week. Among the results obtained was an increase in numbers of total lymphocytes and variety of lymphocyte subsets during exposure to the stressor. Because this type of acute, fear-eliciting stressor is known to involve release of catecholamines (Bandura, Taylor, Williams, Mefford, & Barchas, 1985), this finding is consonant with findings from the epinephrine-injection studies described earlier. In the Wiedenfeld et al. study, a small number of subjects had reduced numbers of lymphocytes during exposure to the stressor; these subjects had elevated levels of salivary cortisol at the end of the treatment session and were slower to attain self-efficacy (Bandura, 1986) or confidence in their abilities to cope with the snake. These results draw attention to the necessity of (a) specifying the nature of emotional stimuli and (b) identifying neuroendocrine mediators of psychoimmunological effects.

In summary, acute stressors have been shown to elicit mixed effects: In some studies, lymphocyte numbers increased, whereas in others they decreased; when assessed, the functional capacity of immune cells tended to be reduced. Acute stressors are likely to be associated with activation of both the sympathetic and adrenocortical stress systems; the differing immunologic effects of these systems may account for the diverse findings.

Chronic Stress

Thus far, relatively little research has considered the effects of chronic stress on immune function. This is unfortunate because there is evidence from animal research (Monjan & Collector, 1977) that effects of stress on immunity may change over time. One exception is the work of Andrew Baum and associates, who are assessing stress effects on residents of the area surrounding the Three Mile Island (TMI) nuclear power plant, site of a serious accident in 1979. Stress levels remain high in this area for several reasons (Baum, Schaeffer, Lake, Fleming, & Collins, 1985): Radioactive gas and water remained trapped inside the containment building for some time following the accident; residents worry about future health consequences of the accident; and fears concerning the reopening of the reactor persist. Recently, McKinnon, Weisse, Reynolds, Bowles, and Baum (1989) found considerably higher levels of neutrophils and fewer B cells, suppressor and cytotoxic T cells, and NK cells in TMI residents compared with demographically matched control subjects living in another area. McKinnon et al. also found higher antibody titers to HSV and CMV in TMI residents. Degree of neutrophil increase was positively related to urinary catecholamine levels, whereas numbers of lymphocytes and NK cells tended to be negatively related to catecholamines.

Unemployment, if prolonged, is a chronic stressor that has been shown in epidemiologic studies to affect mortality and morbidity (Brenner, 1979). A recent study conducted in Sweden examined effects of unemployment on immune function (Arnetz et al., 1987). Subjects were women who had lost their jobs several months before the study began. All received unemployment benefits from the state amounting to 90% of their previous pay; thus the stresses that they were enduring were presumably strictly psychological, rather than resulting from inadequate diet, poor housing, or other physical effects of loss of pay. Subjects fell into three categories: those who were unemployed and receiving the standard benefits package; those who were unemployed, receiving the standard benefits package, and receiving an intervention designed to reduce the psychosocial effects of unemployment; and a control group of employed women recruited from the same geographic region. After nine months of unemployment, both unemployed groups showed reduced lymphocyte response to PHA and a purified protein

derivative (PPD) of tuberculin. No differences were observed in enumeration of lymphocyte subsets, in serum cortisol, or in reported health status.

Kiecolt-Glaser, Glaser, et al. (1987) examined the effects on immunity of the chronic stress associated with caring for relatives afflicted with Alzheimer's disease. (This might also be considered an interpersonal stressor, discussed in the following section. Similarly, the effects of marital quality on immunity, described in the following section, can be considered within the domain of chronic stress). Compared to sociodemographically matched control subjects, caregivers had higher antibody titers to EBV (again, presumably reflecting impaired cellular immunocompetence) and lower percentages of total T lymphocytes and helper T cells, with lower helper:suppressor T-cell ratios. There were no differences in percentages of NK cells. The two groups did not differ significantly in self-reported health, use of cigarettes or alcohol, or in nutrition as indicated by protein assays. A small but statistically significant difference in the amount of sleep reported was observed; however, amount of sleep was not correlated with any of the immune measures.

Thus, the few available data concerning the effects of chronic stress on immunity fail to demonstrate adaptation or compensation on the part of the immune system. Prolonged stress may result in prolonged immunosuppression, the consequences of which could conceivably be severe. Additional research in this area is clearly needed. Effects of occupational stress, economic hardship, and other protracted stressors need to be studied, and interventions developed to mitigate possible adverse effects on health.

Stress Accompanying Social Disruption

Disruption of the social environment can be highly stressful because attachment to others and the social support gained from such attachment is a fundamental human need. Although some social-disruption stressors are acute (e.g., bereavement) and some, chronic (e.g., loneliness, marital distress), social disruption is categorized separately in this article because the neuroendocrine underpinnings of disrupted attachment may be unique; for example, there is evidence that endogenous opioids may be involved in attachment (Panksepp, Siviy, & Normansell, 1985) and thus withdrawal of attachment. Furthermore, socially dependent, or sociotropic, depressions may differ from autonomous ones (Beck, 1983; see also Gilbert, 1988) in their biochemical correlates (McKinney, 1985).

Perhaps the most severe human stressor is bereavement following the loss of a spouse or close relative. It has been shown that widows and widowers evidence increased morbidity and mortality in the year following the death of their spouses (Maddison & Viola, 1968). In a number of studies, the immunologic changes accompanying the loss of a spouse have been examined to test the hypothesis that at least some of this effect may be immunologically mediated. Bartrop, Lazarus, Luckhurst, Kiloh, and Penny (1977), found that the lymphocyte response of bereaved subjects to the mitogens PHA and ConA was reduced (compared with the response of control subjects) 6 weeks after the spouses' death. Enumeration measures showed no differences, and no differences were demonstrated for serum concentrations of cortisol, thyroxine, or prolactin. Using a prospective within-subjects design, Schleifer, Keller, Camerino, Thornton, and Stein (1983) examined immunity in a group of men whose wives had terminal breast cancer. In the first 2 months following bereavement, response to mitogens (PHA, ConA, and PWM) was reduced relative to prebereavement values; intermediate responsiveness was observed 4 to 14 months after bereavement. Again, no differences in total lymphocyte, T-cell, or B-cell numbers were found. Reduced NK cell activity—by 50%—has been observed in women who have recently become bereaved (Irwin, Daniels, Smith, Bloom, & Weiner, 1987), compared with an age-matched control group. Irwin et al. also described a prospective study in which NK cell activity failed to change significantly as a result of the husband's death. The small number of subjects employed, in combination with the likelihood that severe stress characterized the period before the death, render questionable the reliability of this negative result. It is noteworthy that changes in depression from pre- to postbereavement were strongly correlated with changes in NK cell activity.

The research team of Kiecolt-Glaser, Glaser, and associates has also reported effects of social-deprivation stress on immunity. Medical students scoring above the median on the UCLA Loneliness Scale (Russell, Peplau, & Cutrona, 1980) were found to have lower NK cell activity and higher antibody titers to HSV than medical students scoring below the median (Glaser, Kiecolt-Glaser, Speicher, et al., 1985; Kiecolt-Glaser, Garner, et al., 1984). Among a population of psychiatric inpatients, those who reported more loneliness had higher levels of urinary cortisol, less NK cell activity, and poorer T-cell response to the mitogen PHA (Kiecolt-Glaser, Ricker, et al., 1984). Kiecolt-Glaser, Fisher, et al. (1987) found that women who had recently (within the previous 6 years) divorced or separated from their husbands demonstrated reduced immunocompetence relative to a control group of married women. They showed reduced responsiveness to PHA, higher EBV antibody titers, and lower percentages of NK and helper T cells. Women who had been separated or divorced for 1 year or less had significantly lower percentages of NK cells and higher EBV titers than the married women. Interestingly, among the separated and divorced women, higher scores on a measure of attachment to the lost spouse and greater length of time since separation were related to lower percentages of NK cells and helper T cells and higher percentages of suppressor T cells. Among the married women, higher EBV titers and lower mitogen response were associated with poorer quality marriages. Although the groups did not differ in terms of cigarette smoking, the divorced and separated women did report drinking significantly more alcohol during the previous week, and demonstrated poorer nutritional status, leaving open the possibility of behavioral rather than emotional mediation of effects.

In a subsequent study examining effects of marital separation on immunity in men (Kiecolt-Glaser et al., 1988), results both consistent and inconsistent with those found in women were obtained. Divorced or separated men had higher antibody titers for both HSV-1 and EBV and more self-reported illness, compared with sociodemographically and age-matched married men. Among married men, higher ratings of marital quality were associated with *higher* numbers of suppressor T cells, as

well as lower EBV titers. Interestingly, among the divorced and separated men, those who had initiated the separation had lower EBV titers than those who had not. Health behaviors did not differ between the two groups, suggesting that emotional factors mediated the effects.

Thus, with few exceptions, social disruption and loneliness appear to be associated with impaired immune function. Psychosocial interventions to increase social support for people lacking it may directly affect immunologically mediated health outcomes.

Depression

A psychological concomitant of some of the stressors discussed in this article, particularly those related to social loss and disruption, is depression. A number of investigators have looked at immune functioning associated specifically with this state. Patients hospitalized with major depressive disorder have been shown to have impaired lymphocyte response to mitogens and lower absolute numbers of B and T cells, as well as higher plasma cortisol levels (Schleifer, Keller, Meyerson, Raskin, Davis, & Stein, 1984). In another study by this group, ambulatory patients with major depressive disorder were compared with a matched control group and a group of inpatient schizophrenics (Schleifer, Keller, Siris, Davis, & Stein, 1985) in an effort to rule out the possibility that effects of hospitalization rather than depression per se had been the factor responsible for the earlier findings. Although response to mitogens did not differ between groups, the number of T cells was decreased in the depressed, but not the schizophrenic, group. These results seem to suggest that severe levels of depression may be necessary to produce significant immunosuppression. However, in a study designed to explore the relationship between severity of depression and degree of immune impairment, Kronfol, House, Silva, Greden, and Carroll (1986) reported decreased lymphocyte response to mitogens in all subjects but no difference between those with high versus low levels of urinary free-cortisol excretion. In a more recent study with a large sample, Schleifer, Keller, Bond, Cohen, and Stein (1989) failed to obtain differences between patients with major depressive disorder and matched controls for lymphocyte response to mitogens, lymphocyte subsets, or NK cell activity; however, an interaction between depression and age was found. Whereas a positive association between age and mitogen response and between age and numbers of helper T cells was demonstrated for nondepressed subjects, no such relationships existed for depressed ones. Among the depressed subjects, higher levels of depression were associated with lower response to mitogens when effects of age and sex were statistically controlled. Schleifer et al. concluded that immunosuppressive effects of depression may be restricted to particular subgroups of depressed patients.

Interestingly, Kiecolt-Glaser and colleagues have demonstrated impairment of the ability of lymphocytes to repair DNA damaged by irradiation in depressed psychiatric inpatients (Kiecolt-Glaser, Stephens, Lipetz, Speicher, & Glaser, 1985). This finding may have important implications for the development of cancers because damaged DNA is an initiator of carcinogenesis.

Even naturally occurring, nonclinical fluctuations in daily mood may have immunologic correlates. In a study of healthy subjects, Stone, Cox, Valdimarsdottir, Jandorf, and Neale (1987) measured salivary IgA antibody response to stimulation with a rabbit albumin antigen three times each week for 8 weeks. Mood was measured with the Nowlis Mood Adjective Checklist (Nowlis, 1965). Secretion of salivary IgA was significantly greater on days when positive mood was reported than on days when negative mood was reported.

Psychiatric conditions other than depression may be associated with particular immunologic states and processes. The Minnesota Multiphasic Personality Inventory (MMPI; Colligan, 1985; Dahlstrom, Welsh, & Dahlstrom, 1972) assesses several personality dimensions, including hypochondriasis, paranoia, masculinity/feminity, mania, and depression. Heisel, Locke, Kraus, and Williams (1986) examined associations between MMPI subscale scores and NK cell activity in a group of college students. Ten of the 12 subscales correlated weakly (*r*s between $-.15$ and $-.30$) but significantly with NK cell activity. In general, better mental health was associated with higher NK cell values.

Personality and Immune Function

Personality traits and coping styles are of particular interest in PNI research because some immunologic diseases are chronic or take much time to develop. Although relatively little basic PNI research has been conducted in this area, the study of traits is common in psychosocial oncology (see section regarding PNI relationships in cancer).

Inhibited and stressed power motivation. The concept of *power motivation* (McClelland, 1975) is a personality variable that may be associated with more frequent illness (McClelland & Jemmott, 1980; reviewed in McClelland, 1989) and poorer immune function (reviewed in Jemmott, 1987). People whose power motive is strong display a strong need to affect or influence others, a need that is stronger than their need for affiliation with other people. Inhibited power motivation is characterized by a high level of activity inhibition or self-restraint. These motivational syndromes are assessed with a projective test similar to the Thematic Apperception Test. Effects of motivational dispositions may interact with stress.

McClelland, Alexander, and Marks (1982) studied the health correlates of power motivation in a population of prisoners. Subjects who displayed a need for power and who reported high levels of life stress had lower IgA concentrations than did other subjects and reported the highest frequency of illness. Similarly, college students who demonstrated inhibited power motivation and achievement-related stress secreted more epinephrine during performance of a stressful task, had lower IgA concentrations, and reported more frequent illness (McClelland, Floor, Davidson, & Saron, 1980). Jemmott et al. (1983) examined the interactive effects of inhibited power motivation and academic stress on rate of secretion of salivary IgA in dental students. Stress and IgA secretion rate were measured five times during the academic year. Mean secretion of IgA was reduced during stressful periods. Furthermore, student ratings of perceived stress in the academic environment were correlated with the magnitude of reductions in salivary IgA. IgA secretion rates in students who exhibited stronger affiliative motives were gener-

ally higher, and students with inhibited power motivation failed to recover after the period of stress. A subsequent study (Jemmott & Magloire, 1988) produced similar findings within a much shorter time frame (about 3 weeks), ruling out seasonal variation as a mediator of the earlier effects. Jemmott and Magloire also found that students who reported superior social support before the exam period displayed consistently higher IgA levels than did their peers.

In another study (McClelland, Ross, & Patel, 1985), students higher in power motivation than affiliation motivation had lower IgA levels 1¾ hr after an exam, relative to those students for whom the reverse was true, and lower levels compared to their own baselines. In another experiment, McClelland and Kirshnit (1989) assessed interactions between motives and stressor types. Subjects were shown one of two films. One film, designed to arouse power motives, had originally been produced to justify the entry of U.S. troops into World War II. Its themes were dominance and aggression. The other film depicted Mother Theresa ministering to the impoverished and ill in India. Its purpose was to arouse the affiliation motive. Although the affiliation film produced greater overall increases in salivary IgA responses, only subjects high in power motivation displayed diminished salivary IgA in response to the power film.

The use of salivary IgA in psychoimmunology research has recently been criticized (Stone, Cox, Valdimarsdottir, & Neale, 1987). One problem is that, whereas concentrations of IgA protein in saliva decrease with decreased flow (as occurs during autonomic arousal), its rate of synthesis increases when salivary flow is stimulated with lemon drops. Another problem is that saliva contains, in addition to IgA protein, an enzyme that degrades it (though degradation can be avoided by using a collection procedure different than the one used in the studies just described). Finally, total IgA may be a poor measure of immune function because only about 1% of IgA protein becomes antibody under challenge. Stone, Cox, Valdimarsdottir, Jandorf, and Neale (1987) recommend measuring antigen-specific antibodies produced in response to stimulation with rabbit albumin, the measure used in their study (Stone, Cox, Valdimarsdottir, & Neale, 1987).

These allegations have been countered (Jemmott & McClelland, 1989). Setting aside arguments concerning the consistency of results obtained—even if they were consistent, Stone et al. (1987) had argued that they could be artifactual, and even if they were not consistent, this in itself would be insufficient reason for discarding the measure—Jemmott and McClelland responded to each of the three arguments presented by Stone, Cox, Valdimarsdottir, and Neale (1987). First, although Jemmott and McClelland did not dispute the charge that salivary IgA levels are inversely related to flow rate, they cited two studies in which the same results were obtained using each of two IgA measures, resting concentrations and secretion rate. Lemon drops or other stimulating agents were not used. Furthermore, the expected effect of stress-induced slowing of salivary flow on IgA concentrations is opposite to the one found: IgA concentrations should be *higher* under stress, not lower. With respect to the second argument, that salivary IgA is degraded during or following collection, Jemmott and McClelland argued that the degradation is unimportant in magnitude; salivary IgA levels are stable over time and have been shown to be related to future illness. Furthermore, IgA levels in saliva collected from a single gland, the procedure recommended by Stone et al., has not been validated in this way. Jemmott and McClelland claimed that examining stimulated, antibody-specific IgA is likely to produce results with low generalizability, particularly when the antigen is rabbit albumin. Total IgA may be more relevant to upper respiratory infection, which is caused by a multiplicity of pathogens, and total IgA has in fact been linked with actual illness outcomes.

This debate may not be resolved in the near future. What can be reasonably concluded at this point is that (a) secretory rates of salivary IgA not gustatorily stimulated are preferable to stimulated measures or measures taken at a single point in time and (b) health data, most appropriately the incidence of upper respiratory infection, ought to be collected in psychoimmunologic studies using this measure.

A recent series of studies examined effects of motive variables on another set of immunologic indices, namely NK cell numbers and activity (Jemmott et al., 1990). In these studies, college students exhibiting stronger power motivation and greater stress had lower NK cell activity than their peers, whereas those reporting less stress and higher affiliation motivation had the highest NK cell activity. In a second study, these results were replicated with subjects who were healthy men around 30 years old. Subjects in a third study were members of a health maintenance organization. In this sample, the stressed power-motive group had marginally lower NK cell activity ($p < .06$) than the other subjects, although the earlier finding of increased activity in the unstressed affiliation-motive group was not replicated.

Thus, there is evidence to suggest that motive-related personality variables may be important mediators of the effects of stress on some aspects of immune function. The relationship of personality variables to a wider variety of immune parameters ought to be examined, particularly given the debate about the appropriateness of the salivary IgA measure for psychoimmunology research.

Locus of control. Locus of control is a person's belief about the degree to which outcomes are generally under his or her own control (internal) or that of others or the environment (external). Kubitz, Peavey, and Moore (1986) explored the relationships between health locus of control, daily-hassles stress, and levels of salivary IgA. Locus of control was assessed with the Health Locus of Control Scale (HLC; Wallston, Wallston, Kaplan, & Maides 1976), which measures locus of control over health outcomes. Although no relationship between daily-hassles stress and salivary IgA was found, an inverse correlation was obtained between salivary IgA and internal locus of control. This finding, that stronger belief in one's ability to control health outcomes was associated with reduced immunocompetence, was surprising. However, an interaction between stress and locus of control also was obtained: Subjects with high internality and high stress had lower levels of salivary IgA than those with high internality and low stress. Thus, the effects of stress may be potentiated by the belief that one is onself responsible for (at least some) outcomes.

Repressive coping. A coping style thought to involve repression,—inattention to, and forgetting of, threatening material—

has been empirically studied by Weinberger, Schwartz, and Davidson (1979). In this study, subjects who were classified as repressors, on the basis of self-report of low distress combined with high need for approval, demonstrated higher autonomic arousal during a stressful task (completing sentences with sexual or aggressive content) than did subjects reporting high distress or low distress but low need for approval. In a recent study of 312 students, Jamner, Schwartz, and Leigh (1988) found repressive coping to be associated with decreased monocyte counts and increased eosinophil counts. Although the decreased monocyte count can be interpreted as indicating immune impairment, the meaning of increased eosinophil counts is unclear.

In a study of psychoimmunologic relationships in a geriatric population (described more fully later), repressive coping was associated with reduced response to mitogens (Brown, O'Leary, and Murasko, 1989). This finding is of particular significance because 50% of subjects in the older sample displayed this pattern; in studies of college students, roughly 10% of subjects display this pattern. The meaning of the pattern of responses that make up the repressive coping construct are not clear, particularly with respect to whether socially desirable responding constitutes self-deception or other-deception (Sackheim & Gur, 1978), and the significance of repressive coping in this population remains to be determined.

Enhanced Immunocompetence Through Psychosocial Intervention

If psychosocial phenomena influence the immune system, it should be possible to design psychosocial interventions that improve immunologic functioning. Some attempts have been made to develop treatments for populations with particular diseases, and these are described later in their disease-relevant sections. In addition, a small number of studies have attempted to improve immunity in healthy populations. One example is a study by Kiecolt-Glaser and colleagues (Kiecolt-Glaser, Glaser, et al., 1985), in which two interventions were administered to a geriatric population. (See the next section for further discussion of psychoimmunologic research with older subjects.) Subjects were assigned to one of three groups: relaxation training, social contact, or no contact. The first group received training in relaxation techniques three times each week for 1 month. Subjects in the social-contact group were visited in their homes by a college student. The third group received no intervention. Subjects did not know of any connection between the interventions and the psychosocial and immunologic assessments.

Following treatment, NK cell lysis activity was significantly enhanced, and HSV antibody levels were significantly reduced, in the relaxation-training group. Some enhancement in response to mitogens was seen in all three groups. No other change in immune function was observed in either the social-contact or no-treatment groups. Kiecolt-Glaser, Glaser, et al. (1985) suggested that the social-contact intervention may have failed to enhance immune responses because pretreatment levels of distress were not high, because these subjects were residents of independent living facilities, and because they may have felt little need for additional social contact.

A stress-management intervention to reduce effects of examination stress was employed in a study of medical students (Kiecolt-Glaser et al., 1986). Immunologic measures included percentages of helper T and suppressor/cytotoxic cells and NK cell activity. Although no differences in any immune measure were observed between subjects who had received the intervention and a group of control subjects, the amount of relaxation practice was positively associated with the percentage of helper T cells.

On the basis of a model of psychotherapy in which disclosure and cognitive processing of negative thoughts and feelings enhances well-being, Pennebaker, Kiecolt-Glaser, and Glaser (1988a) asked undergraduate subjects to write essays about either traumatic or neutral experiences and then examined subsequent immunologic and health outcomes. Essays were written in 20-min sessions on each of four consecutive days. Lymphocyte response to two mitogens, PHA and ConA, was determined at three sample points: the day before beginning to write, the last day of writing, and 6 weeks after writing. Health-center medical records were examined for two periods: the 5 months prior to the study and the 6 weeks between writing essays and the follow-up assessment. Subjects who had written about traumatic events showed greater enhancement of mitogen response (significant for PHA but not ConA) than those who had written about neutral subjects. Furthermore, trauma-disclosing subjects made significantly fewer subsequent visits to the health center than did control subjects. Evidence was also obtained for greater immunoenhancement in subjects who had written about topics that they had "actively held back" from discussing previously.

Neale, Cox, Valdimarsdottir, and Stone (1988) subsequently argued that the results of Pennebaker et al.'s (1988a) study may have been misinterpreted and gave three reasons. First, control subjects manifested higher PHA response prior to treatment, and an analysis of covariance (ANCOVA) may have rendered the effect nonsignificant. Second, the apparent effect of treatment was accounted for primarily by reductions in the control group's response, not enhancement of the treated subjects' response. Third, the reductions in health-center visits may not have been immunologically mediated, as there was no significant difference between groups at the 6-week follow-up. In rebuttal, Pennebaker, Kiecolt-Glaser, and Glaser (1988b) responded that (a) between-group differences before treatment were nonsignificant, and ANCOVAs produce even higher significance levels; (b) the control group's decline in PHA response may have been due to differences in lymphocyte storage time before and after the intervention, a factor obtaining in both groups; (c) results of internal analyses were consistent with the interpretation that the disclosure treatment affected the immune response; and (d) although immune changes were not significantly correlated with number of health-center visits, the immune system is too complex to render acceptable the null hypothesis that there is no causal connection between the two.

In summary, there is some evidence for immunologic enhancement in subjects who are trained in relaxation and who practice it faithfully. It cannot at this time be concluded with certainty that disclosure of trauma is immunologically beneficial. However, because the implications of an immunologic effect of this type of intervention are considerable, replication of the finding would be valuable.

A Special Population: The Aged

Psychoimmunologic relationships may vary for different populations, for example, particular age groups. The burgeoning older population has begun to receive attention recently. Decrements in T-cell function and increased variability in NK cell activity have been reported with advancing age, although B-cell numbers and function seem to be unimpaired (reviewed in Solomon et al., 1988). Furthermore, psychoimmunologic relationships may differ between older and younger people (Schleifer et al., 1989).

Social support is particularly important to the well-being of older adults, and in one large-sample study (Thomas, Goodwin, & Goodwin, 1985) a positive relationship was found between strength of existing social bonds and two measures of immunocompetence: lymphocyte numbers and response to the mitogen PHA. These relationships were significant only for women, however. Social support in this study was expressed as the existence of frank and confiding relationships, a fact of relevance for interventions employing social disclosure (Pennebaker et al., 1988a).

Solomon et al. (1988) are currently following a group of healthy people between 65 and 89 years old and a control group of younger people. Assessments of psychological functioning, as well as baseline and stimulated NK cell activity and NK cell numbers, are performed every 6 months. Included among the psychological measures is one of "hardiness." The hardy personality (Kobasa, 1979; Kobasa, Maddi, & Kahn, 1982) is thought to be characterized by three components: the belief that one is in control of outcomes, a commitment to life endeavors, and the feeling that change is challenging. Solomon et al. (1988) initially found that, among the older group, beta-endorphin-stimulated NK cell activity was significantly positively correlated with hardiness; however, this finding was not replicated at the next assessment (Solomon, 1988). The low levels of distress reported by subjects in this study may account for the low or inconsistent relationships obtained.

Brown, O'Leary, and Murasko (1989) examined both trait and state psychosocial measures in association with a comprehensive immunologic assessment. Subjects, who ranged in age from 67 to 93, were interviewed three times; interviews were 2 months apart. Trait psychological measures were correlated with the averaged immune measures; Brown et al. found that repressive copers showed reduced lymphocyte response to the mitogens PHA and ConA and that enhanced gamma-interferon production by stimulated lymphocytes was demonstrated in subjects with more control of anger, and less anxiety. Correlations were performed between changes between assessment points in state psychosocial measures and changes in the immune measures, and it was found that increases in loneliness were associated with reductions in lymphocyte response to PWM and that increases in perceived stress and hopelessness were associated with reductions in unstimulated NK cell activity. Because several psychosocial and immunologic measures were included, findings from this very exploratory study require replication.

In another longitudinal study of psychoimmunologic relationships in older individuals, Judith Rodin and her colleagues are focusing on perceptions of control and optimism (Rodin, 1988). Thus far, Rodin's group has demonstrated that older subjects whose helper:suppressor (T4:T8) cell ratios are in the lower quartile tend to attribute negative events to aspects of themselves that are stable and likely to affect many things—an attribution style associated with the development of depression (Seligman, Abramson, Semmel, & von Baeyer, 1979).

Clearly, psychoimmunologic research with special populations is only beginning. A focus on issues relevant to particular age groups, including children, is sure to be fruitful. Immune function changes with age (for example, it generally seems to become more variable), and it is quite possible that the psychosocial factors connected with immunity also will be different for different age groups. Examination of differences in psychoimmunologic relationships between various healthy populations may provide data of interest both to psychologists and immunologists.

Psychosocial Factors in Disease

Not all people who are exposed to infectious pathogens become ill. This realization has led to a search for "host resistance factors," which include psychosocial and behavioral phenomena (Jemmott & Locke, 1984). The effect of life-event stress on susceptibility to disease was examined in a number of early studies (e.g., Holmes, Hawkins, Bowerman, Clarke, & Joffe, 1957). Patients generally reported a greater number of stressful life events during the preceding year or several years before disease onset than did healthy control subjects. This literature is voluminous and has been reviewed elsewhere. Furthermore, there are a number of problems in interpreting research utilizing retrospective self-report of stress. The following review of stress and human illness is restricted to studies in which immune parameters were examined directly.

Cancer

Much research on psychosocial factors in cancer incidence and progression has been concerned with providing links between psychosocial factors and disease outcome, and most studies have not examined immunologic mediation. A host of such studies have, however, yielded evidence suggesting that a constellation of traits and coping styles are associated with the development of cancer, more rapid progression, and worse prognosis (Derogatis, Abeloff, & Melisaratos, 1979; Greer, Morris, & Pettingale, 1979; Morris, Greer, Pettingale, & Watson, 1981; Rogentine et al., 1979; Shekelle et al., 1981; Temoshok, 1987). People who report being fatigued, less distressed, less hostile, helpless, and who fail to express negative affect seem to be at greater risk. Sandra Levy and colleagues examined immunologic parameters in a study of psychological factors influencing breast cancer outcomes (Levy, Herberman, Maluish, Schlien, & Lippman, 1985). In this study, psychosocial factors were examined with respect to NK cell activity and cancer outcome. NK cells are thought to be an important host defense against cancer, and as noted earlier, changes in NK cell activity have been observed with increased stress. Levy et al. (1985) found that patients who reported less distress and who seemed better adjusted to their illness, who reported high levels of fatigue on the Profile of Mood States (POMS; McNair, Loor,

& Droppleman, 1971), and who perceived less social support in their environment, showed less NK cell activity. Lower NK cell activity was in turn related to a higher number of positive lymph nodes at diagnosis, the biological endpoint used in the study. Three months later, after cancer treatment had begun, fatigue and low social support remained marginally significant predictors of NK cell activity (Levy, Herberman, Lippman, & D'Angelo, 1987). In a 7-year follow-up of 36 patients with recurrent disease, Levy, Lee, Bagley, and Lippman (1988) examined predictors of ultimate survival time. At this time, 24 of the 36 patients had died. Survival time was predicted by one psychological factor: the expression of more joy at baseline testing. Because other significant predictors were number of metastatic sites, length of disease-free interval, and physician prediction of longer survival, an alternative explanation is that patients who perceived their doctors to be more hopeful (hope that may well have been based on biological factors) may have felt more joy than other patients. Thus, biological factors, such as degree of metastasis and disease-free interval, may have accounted for both doctor hope and patient joy. Arguing against this is the absence of correlation between patient joy and the doctor's stated prognosis, although more joy was associated with fewer metastatic sites. In any event, the finding that joy, rather than distress, was prognostically significant was contrary to Levy et al.'s prediction.

Levy et al. (1989) recently reported some psychosocial correlates of persistently low NK cell activity in a healthy young adult population. This putative syndrome may be a marker of the so-called chronic fatigue syndrome (CFS), in addition to being potentially related to the eventual development of malignancy. CFS, which most often seems to affect young adults, has been hypothesized to be caused by EBV, possibly in combination with another viral cofactor. However, the association between EBV and symptoms of the disorder is not reliable. Persistently low NK cell activity is associated with chronic feelings of fatigue or remittent, low-grade fever, or both; these symptoms are commonly reported among CFS patients.

According to clinical reports, psychological stress often accompanies these symptoms. Levy and her associates are currently conducting a longitudinal study of healthy young adults; psychosocial and immunologic assessments are included in the study. In their first report, Levy et al. (1989) divided subjects who had undergone three immunologic assessments into high and low NK-cell activity groups on the basis of two sets of criteria, one stricter for low-NK categorization. Levy et al. found that subjects with low NK cell activity (defined strictly, this category included approximately 15% of the 88 subjects) differed significantly from the other subjects in several ways: They were younger, had fewer NK cells, excreted half as much urinary norepinephrine, and were more depressed. Marginally significant in the low-NK group were increased daily-hassles severity, lower urinary epinephrine excretion, and more fatigue. Interestingly, the low-NK group also displayed elevated titers to one of three antibodies to EBV that were tested. Levy et al. noted that this association could be due either to effects of EBV on NK cell activity or to poorer NK cell function, permitting escape of EBV. In logistic regression analyses, only age and hassles severity were significant predictors of NK status.

In a study of cutaneous malignant melanoma, psychological factors were examined in relation to a number of relevant immunologic measures (Temoshok, 1985; Temoshok et al., 1985). Temoshok et al. hypothesized that the Type C personality, characterized by the tendency to suppress the expression of emotion, would be associated with diminished immunologic defense against the cancer and with poorer prognosis. Temoshok et al. measured Type C personality by using a structured interview in which the subject was asked to describe recent events during which specific emotions were experienced. The interviews were rated in terms of subjects' emotional, behavioral, physical, and cognitive reactions to the events. It was indeed found that reduced expression of emotion was associated with more rapid tumor mitosis and poorer infiltration of lymphocytes at the site of the cancer, and with greater tumor thickness, all indicators of poorer prognosis in cutaneous malignant melanoma.

Genital Herpes

Cellular control over latent herpesviruses is impaired under conditions of stress, leading to increases in levels of herpes antibody in stressed individuals. Presumably this effect, if large enough, could result in actual outbreak of lesions. In fact, effects of stress and coping on immune function and outbreak of genital herpes have recently been investigated (Kemeny, Cohen, Zegans, & Conant, 1989). Thirty-six subjects with recurrent HSV were followed for 6 months. A number of factors were assessed in monthly interviews, including psychological stress, mood, health behaviors, other possible HSV triggers, HSV recurrences and (in half of the subjects) proportion of T4 (helper) and T8 (suppressor and cytotoxic) cells.

The study yielded support for the hypothesized operation of psychological processes in herpes recurrence. An aggregate stress index was significantly negatively related to proportions of T4 and T8 cells. More negative mood, however, was significantly associated with fewer T8, but not T4, cells. This was true for all of the mood states examined in the study: anxiety, depression, and hostility. Semipartial correlations were performed to assess the unique contributions of the two sets of psychological variables to immunity. Although stress accounted for approximately twice the unique variance in T4 levels that mood did, mood accounted for 2 to 10 times the variance in T8 levels that stress did. Kemeny et al. (1989) found that recurrence rate was unrelated to T4 cell levels but was negatively correlated with T8 levels (presumably accounted for by the cytotoxic, rather than suppressor, cells expressing the CD8 receptor). Although psychological variables were unrelated to number of recurrences in direct tests, an analysis of the relationship in subjects who had not experienced a large number of infections (a physiological trigger for lesion outbreak) revealed that higher levels of depression, but not stress, were associated with more recurrences. Thus, a hypothesized pathway from depression to diminished T8 cell levels to herpes recurrence was posited, although this model did not receive consistent support in further analyses. Month-to-month changes in depressive mood did not predict time of recurrence, possibly because subjects' depression levels were very stable over time, restricting the range of values in the correlation. Although a need for further research in this area is indicated, Kemeny et al.'s study

represents an admirable first effort to explicate the complex relationships contributing to disease course in herpesvirus.

Autoimmune Disease

Autoimmune disease differs from infectious disease in that it is characterized by enhanced activity in some components of immunity, and thus prognosis is improved when the immune response targeted against self-agents is reduced. Consequently, if negative affective states are associated with worse disease outcome (and the evidence that exists seems to indicate that this is generally the case), then negative affect ought to be associated with greater response in the relevant immunologic parameters, and psychological improvement ought to be associated with reduced response. In fact, for the two diseases described below, there is suggestive evidence for malfunction—underresponse—in the suppressor T-cell system, associated with failure to control autoimmune processes.

Rheumatoid arthritis (RA). This is the most common polyarthritis, with prevalence estimates ranging from 1% to 4% of the population. It can be a severely painful and disabling disease. RA is an autoimmune disorder whose precise etiology is not yet clearly understood. The disease seems to have its basis in an inflammatory response possibly initiated by an infectious agent such as EBV. Many, although not all, patients demonstrate in their serum *rheumatoid factor,* a type of immunoglobulin that is directed against other immunoglobulins; that is, rheumatoid factor attacks other antibodies as though they were pathogens. Inadequate functioning of the suppressor T-cell system has been observed and may be causally implicated (Abdou, Pascual, & Racela, 1979; Decker et al., 1984).

Effects of psychological factors on immunologic activity in RA have been studied in several ways. Early research (reviewed by Moos, 1964; Solomon, 1981) indicated the prevalence among RA patients of a personality pattern characterized by inhibition of emotional expression and dependence. Other research indicated that stressful life events tended to precede the onset of RA (reviewed in Anderson, Bradley, Young, McDaniel, & Wise, 1985; Weiner, 1977). In a recent study of stress and coping in female RA patients, Zautra et al. (1989) found that greater psychological distress was associated with lower proportions of T cells and major life events, with lower helper:suppressor T-cell ratios. Both of these results were unexpected; however, subjects with greater numbers of small stressors had higher percentages of B cells (which are elevated during inflammatory phases in the disease). No relationship between immune indices and disease activity was observed.

To date, most researchers of the immunologic mediation of psychological effects have used intervention studies, in which psychosocial treatments were evaluated in terms of immune function. These interventions involved the use of cognitive–behavioral techniques and were focused on stress management.

A comprehensive psychosocial intervention for RA was tested by Lawrence Bradley and colleagues (Bradley et al., 1985, 1987). Subjects were assigned to one of three treatment groups: (a) a cognitive–behavioral program that included thermal biofeedback at painful joints, training in deep muscle relaxation, and behavioral goal setting; (b) a nondirective social-support condition; or (c) a no-treatment control. Only the cognitive–behavioral intervention was effective, resulting in increased joint temperature, reduced pain behavior during a videotaped 10-min movement sequence, less pain, improved provider assessment of disease activity (presumably reflecting inflammatory processes occurring in the joints), and lowered levels of rheumatoid factor. A measure of "arthritis helplessness," a hypothesized psychological mediator of treatment effects, did not change as a result of treatment.

A similar intervention has recently been evaluated through assessment of immune function at the cellular level (O'Leary, Shoor, Lorig, & Holman, 1988). In this study, a cognitive–behavioral treatment, which included pain- and stress-management training and behavioral goal setting, was compared with a bibliotherapy control. Treated subjects demonstrated reduced pain and improved joint condition, as determined by examinations conducted by rheumatologists who were blind to the patients' treatment groups. No changes in numbers of T-cell subsets or lymphocyte response to mitogens were observed. The hypothesized psychological mediator of change in this study was perceived self-efficacy. Self-efficacy, as described earlier, is a person's self-perceived ability to cope effectively with particular stressors, in this case pain, physical functioning, and general arthritis symptoms. Self-efficacy variables correlated with the relevant outcome variables, supporting the mediating role of the construct. Furthermore, perceived ability to manage pain was positively correlated with number of suppressor cells and negatively correlated with helper:suppressor T-cell ratios at the end of treatment, although the meaning of this association in the absence of treatment effects on cellular immunity remains unclear.

In summary, evidence from psychosocial RA interventions suggests that, although serum measures of immune function may not be related to psychological factors, local inflammatory processes may be. Psychological treatment has been shown to result in lower sedimentation rates (Achterberg, McGraw, & Lawlis, 1981) and reductions in joint impairment, both of which are indices of local inflammation. That local factors are more closely associated with psychosocial ones is not surprising in view of the possibly low correlation between serum and local measures of immunologic functioning in the disease.

Multiple sclerosis. This is a chronic illness in which the myelin sheaths of nerve cells are destroyed. It is accompanied by immunologic changes, although it is not known whether the changes are causes or effects of demyelination. As with RA, there is evidence for dysregulation of the suppressor/cytotoxic lymphocyte population. The role of psychological factors in the immunologic as well as neurologic manifestations of the disease were recently explored by Foley et al. (1988). Patients were divided into low and high groups for both anxiety and depression on the basis of median splits. Because anxiety and depression were highly correlated in the study, there presumably was considerable overlap between both high groups and both low groups. Those who were more depressed had higher absolute numbers and percentages of T4 (helper) cells; high-anxiety patients had higher absolute numbers of T4 cells. However, there was no difference between groups in numbers or percentages of suppressor/cytotoxic lymphocytes. Furthermore, no relationship between psychological distress and physical impairment was observed. The significance of these findings remains un-

clear, although further explication of psychoimmunologic relationships is warranted because the immunologic aspects of multiple sclerosis are not yet understood.

AIDS

HIV is the etiologic agent of AIDS. The virus produces its immune-suppressing effects by destroying the helper T cells. The virus also enters, but does not always destroy, the monocyte/macrophage, which thus may become a reservoir for the virus, and which is the likely route of transport to the brain. HIV is spread by sexual contact, infected blood, or perinatally from infected mother to infant. As the immunologic aspects of HIV become better understood (see Fauci, 1988), the prospects for managing the disease will doubtless improve. In the meantime, it is widely believed that the mortality rate from AIDS, and even from HIV infection, will approach 100% over the course of several years. Infected persons, following asymptomatic periods that typically last for years, eventually will develop any of a variety of symptoms and opportunistic diseases and be diagnosed with AIDS-related complex or ARC (see Redfield & Burke, 1988). A diagnosis of AIDS is received when any one of several conditions develop; these include *Pneumocystis carinii* pneumonia, an opportunistic neoplasm such as Kaposi's sarcoma or non-Hodgkins lymphoma, dementia, or wasting syndrome in the presence of HIV infection.

In recent years, investigators have begun to examine psychosocial influences on the progression of HIV infection. Most of this work is currently in progress. Several pathways for effects of psychosocial factors on AIDS progression exist (reviewed in Solomon, 1989; Solomon, Kemeny, & Temoshok, in press). They include reactivation of latent viruses (e.g., herpesviruses), causing proliferation of helper T cells and subsequently of HIV; reduction of numbers and functioning of peripheral lymphocytes due to neuroendocrine processes (e.g., cortisol); and more productive initial infection due to host condition at the time of infection.

Solomon and Temoshok (1987) conducted an early study in San Francisco and reported effects of psychosocial factors on immune function in persons with AIDS and ARC. They found that persons with high levels of dysphoria, as indicated by scores on an anxiety scale, a hopelessness measure, and the POMS, had higher numbers of both polymorphonuclear cells and total lymphocytes. Furthermore, subjects with lower scores on the hardiness scale had greater numbers of lymphocytes. These results might be taken to indicate that less adequate psychological defenses are associated with impaired defense against the HIV virus and thus greater numbers of opportunistic infections. The body's response to these infections would in turn result in greater numbers of PMN cells. However, because the virus selectively destroys lymphocytes, the finding of increased numbers is difficult to interpret.

In another study by this group (Solomon, Temoshok, O'Leary, & Zich, 1987; Temoshok, Zich, Solomon, & Stites, 1987), 18 persons with AIDS underwent an intensive psychosocial interview followed by weekly assessments of immune function and emotional response for 5 weeks. Multiple regression analyses revealed that, after diagnosis (*Pneumocystis carinii* pneumonia or Kaposi's sarcoma) and time since diagnosis had been entered, POMS scores indicating less tension and anxiety were associated with larger absolute numbers of helper T cells. Other psychosocial factors associated with more helper T cells included less POMS depression–dejection, less POMS fatigue–inertia, and less POMS anger–hostility. Correlated with cytotoxic T cells, which in theory may compensate for losses of helper T cells, were less stress from illness, less POMS fatigue–inertia, less stress due to factors other than illness, not doing unwanted favors, and less POMS tension–anxiety. When stress from illness was controlled in a fourth-order correlation, only the variable of not doing unwanted favors remained significant. Similarly, absolute numbers of suppressor cells were positively associated with more fitness and regular exercise, not doing unwanted favors, less POMS fatigue–inertia, and withdrawing to nurture the self. In addition to cytotoxic T cells, virucidal cells and NK cells were both considered to be possibly able to compensate for lost helper T cells. Greater absolute numbers of virucidal cells were associated with not doing unwanted favors, less POMS fatigue–inertia, less POMS tension–anxiety, less stress from factors other than sickness, and higher scores on an "upness" scale; NK cell numbers were related to nurturing the self, less preoccupation with AIDS, and less POMS fatigue–inertia. NK cell activity was increased in subjects who regularly exercised. Levels of P24 antigen (part of the HIV virus whose presence reflects viral activation) were also examined with respect to psychological factors; P24 antigen was elevated in the presence of more depression, less vigor, more fear, less of a self-rated sense of humor, and less active coping. Serum cortisol failed to demonstrate significant associations with any of the immunologic parameters.

In another component of this investigation (O'Leary, Temoshok, Jenkins, & Sweet, 1989), an analysis of relationships between immune function and autonomic reactivity during the reliving of emotional events revealed that subjects who evinced greater skin conductance and finger temperature responses had superior NK cell cytolytic capacity (measures averaged across the 5 weeks). At a 3-year follow-up, autonomic reactivity predicted survival after disease, months since diagnosis, and number of helper T cells at the initial interview were controlled. NK cell activity was marginally predictive of survival, suggesting that it may have mediated the effects of reactivity on survival. Greater peripheral arousal was interpreted to reflect a more autonomically reactive temperament, which ought to be associated with greater and more frequent release of catecholamines. Acute administration of catecholamines is associated with enhanced NK cell activity, as described earlier, and this interpretation is also consonant with the finding by Levy et al. (1989) of enhanced NK cell activity in subjects with high levels of urinary norepinephrine. This finding has potential relevance for cancer research and corroborates the previously mentioned findings of stoicism and low emotionality in patients with worse cancer outcome.

In a larger, longitudinal study by this group (Temoshok et al., 1988; Temoshok, Solomon, Jenkins, & Sweet, 1989), relationships between psychosocial, immunologic, and neuropsychologic factors were assessed in 100 seropositive, symptomatic gay men at two points in time, 6 months apart. At the first assessment, absolute numbers of T4 (helper) cells were associated with more POMS tension–anxiety, trait anxiety, anger–hostility,

and loneliness. In addition, more reported control of emotion was associated with more T4 cells and more NK cells. Percentages of T4 cells were positively correlated with more anxiety, less emotional control, and greater loneliness. At the second assessment, greater emotional control was associated with more NK cell activity, and greater loneliness was associated with higher percentages of T4 cells. These findings are at odds with those obtained by the same investigators in subjects with AIDS (Solomon et al., 1987; Temoshok et al., 1987); Temoshok et al. (1988, 1989) speculated that different psychoimmunologic relationships may obtain at different stages of the illness.

Kemeny et al. (in press) based in Los Angeles, are following HIV-infected gay men, as well as a control group of uninfected gay men, to assess the contribution of psychosocial factors to HIV progression. Forty-five subjects who had lost one or more close friends to AIDS during the preceding year were compared to 45 age- and serostatus-matched nonbereaved men. Immunologic assessments included lymphocyte response to PHA; levels of serum neopterin, a measure of immune activation; and percentage of helper T cells and of NK cells. No differences between bereaved and nonbereaved groups were found for any immune parameters among either the seropositive or seronegative subjects; depressed mood following bereavement was not related to immunologic factors in seropositive men but was associated with lower levels of NK cells in uninfected men; in nonbereaved seropositive subjects, depressed mood was associated with several signs of immune dysfunction: lower responses to mitogen, fewer helper T cells and more suppressor T cells.

Efforts to improve immune status through psychological or behavioral intervention have been disappointing. In a controlled study, Coates, McKusick, Kuno, and Stites (1989) failed to demonstrate effects on lymphocyte subset enumeration, NK cell activity, or mitogen response in a group of men given training in relaxation and other stress-management skills. Coates et al. listed several possible reasons for this result: sadness at the termination of the group intervention may have affected the posttreatment assessment; the intervention may have been insufficiently potent; and stress may have in certain ways been increased by the intervention, which had an educational component designed to reduce risk-related behavior.

A research group in Florida has begun to examine the efficacy of physical exercise as a behavioral intervention to improve immune function in HIV-spectrum illness (Laperriere et al., 1988; Laperriere, Schneiderman, Antoni, & Fletcher, 1990). Subjects were healthy gay men, some of whom were found to be positive for HIV antibody during the study. They were randomly assigned to three sessions of aerobic exercise per week or to a control condition. Initial assessments were conducted after 4 weeks of training. In subjects who were not infected with HIV, exercise produced increases in T4 (helper) cells and B cells, as well as enhancement of lymphocyte response to PHA and PWM. Only a modest increase in numbers of T4 cells was observed in subjects whose antibody status was positive. This preliminary finding corroborates Coates et al.'s (1989) negative result for stress-reduction therapy and suggests that such interventions may be less (or non-) effective in subjects who are harboring the virus. Interestingly, most of the subjects in Laperriere et al.'s study demonstrated an increase in white blood cells at the time of disclosure of their antibody status (the only group that did not were the antibody-negative exercisers), reflecting the anticipatory stress of receiving this information.

In another report, immunologic assessment was performed on subjects at five time points during a 3-month period, and effects of receiving news of HIV antibody status were examined (Ironson et al., 1988). Within 72 hr of receiving the news, subjects showed a reduction in NK cell numbers, regardless of whether their antibody status was positive or negative. Reduced lymphocyte response to mitogens and NK cell activity were also observed within 10 days. Within 72 hrs, increases in the number of white blood cells were observed (perhaps ascribable to sympathetic arousal and catecholamine release in the presence of fear). A later report (Ironson et al., 1990) indicated a dissociation between psychological and immune factors in seropositives, with immune suppression preceding antibody notification in seronegatives.

In summary, evidence does exist for the influence of psychosocial factors on immune function in HIV-spectrum illness, although relationships may differ or be less reliable in this population. The immunologic concomitants of HIV infection and of each of a host of opportunistic conditions may introduce variability that can mask psychoimmunologic relationships (or relationships may depend on the illness and immune profiles of subjects). Furthermore, different psychoimmunologic processes may prevail at different disease stages. The continued exploration of factors influencing outcome in this illness, as well as the development of effective interventions for the HIV-infected population or subpopulations, are particularly important tasks for PNI researchers as medical advances continue to be made. Jointly, medical and psychological intervention may ultimately prolong the life of those affected.

Conclusions and Future Directions

In this article, I have reviewed the evidence for psychosocial influences on a variety of aspects of immune function and on several disease processes. The common perception that negative affect is associated with suppressed or less effective immune function, and that positive affect is associated with enhanced function, is not uniformly accurate. One exception is the increase in circulating lymphocytes observed in the presence of catecholamines and in connection with acute fearful stress. Another exception to this pattern is found for NK cell activity, which is enhanced in subjects who are excreting more urinary catecholamines and in more sympathetically reactive subjects (people with AIDS). This latter finding (and possibly the former as well) are particularly interesting in that they suggest that ongoing, dispositional sympathetic reactivity may be beneficial—an assumption that cannot be made on the basis of single-stressor or injection studies alone. For cancer, there is evidence that emotionality and a fighting spirit are prognostically beneficial and that stoicism, fatigue, and emotional inexpressiveness are harmful. Evidence for deleterious effects of depression, helplessness or hopelessness, and social loss also exists (Contrada, Leventhal, & O'Leary, 1990). These effects may be mediated, at least in part, by the beneficial effects of catecholamines or harmful effects of cortisol on NK cell function; in fact, the possible independence of these two pathways

may account for the confusing and contradictory findings in the psychosocial oncology literature (Contrada et al., 1990). In autoimmune disease, distress may be associated with immune suppression in the form of reduced suppressor-T-lymphocyte function.

That catecholamines and activation of the SAM system during acute stress should be associated with enhanced numbers of peripheral leukocytes makes sense when considered in an evolutionary context. An organism engaged in a fight-or-flight response is likely to be in danger of being wounded. Because wounds may become bacterially infected, redistribution of leukocytes to the periphery seems an adaptive response. Neutrophils, which are especially important in bacterial defense, are particularly raised in number following epinephrine injection (Gader & Cash, 1975) and following corticosteroid administration, which generally reduces peripheral leukocyte numbers. Although lymphocyte function is reduced following epinephrine administration (as indicated by mitogen response), this may be corrected over time as the beta-adrenergic receptors on lymphocytes become down-regulated following prolonged exposure to catecholamines (Feldman, Limbird, Nadeau, Fitzgerald, Robertson, & Wood, 1983).

Only a few of the studies reviewed here—those involving RA—used painful stressors, which may be more likely to involve opioid activation; no study assessed opioid activation directly. Research utilizing painful stress in humans, particularly studies that assess opioid activation as well as activity in other neuroendocrine systems, would be interesting, as psychoimmunologic effects involving opioid activation have been demonstrated in animals (Maier, Laudenslager, & Ryan, 1985).

Those stressors most likely to generate HPAC activation and cortisol release, namely, chronic stress, depression, and social deprivation, seem to be consistently immunologically suppressive, consonant with studies of cortisol effects on immunity. That the immune response should be impaired during the conservation–withdrawal response may in part reflect lymphocyte redistribution into areas of storage and, in evolutionary terms, may reflect less need for immunologic defense during exposure to these types of stressors.

Serum cortisol assays were included in a number of studies reviewed; in general, the results were unsatisfying. Corticosteroid administration and cortisol added to immune assays produced a variety of suppressive effects. Cortisol is released in response to distress, and many studies have demonstrated relationships between distress and suppressed immunity. However, attempts to demonstrate cortisol mediation of these relationships have not been successful. Because of the lability of the HPAC system and intersubject variability, the use of a single plasma sample for the assessment of HPAC activity is problematic. Intersubject variability in resting levels may occur because of the time of day, the subject's reproductive state, differential percentages of free versus protein-bound levels of cortisol, and genetic variables (Levine & Coe, 1985; Schlechte & Coffman, 1985). Twenty-four hour urinary cortisol assessments, cortisol response to challenge, and more careful timing of sample collection with respect to psychological events may indicate stronger mediating roles for cortisol than have as yet been demonstrated.

These examples illustrate the importance of examining different components of psychoimmunologic processes individually and, preferably, at the same time. It is, in fact, overly simplistic to speak of immune enhancement or immune suppression in global terms for processes as complex as the interactions between and within subjective states and the nervous, endocrine, and immune systems. Furthermore, effects may change over time (Monjan & Collector, 1977). A similar tendency to oversimplify exists in the psychosocial domain. The term *stress* is now used to encompass a vast number of differentiated emotional states. At the biochemical level, a large number of stress-related hormones neurotransmitters, and neuromodulators may accompany different subjective states and affect immune function. Within the autonomic nervous system alone, there is evidence that peripheral autonomic signs distinguish individual emotional states (Ekman, Levenson, & Friesen, 1983; Schwartz, Weinberger, & Singer, 1981). To the extent that individual emotions produce different physiological effects, those emotions ought to have differing immunologic consequences. Research in which potential mediators are assessed through biochemical assay and related to type and degree of immunologic change is desirable. Another issue concerning the psychosocial components of psychoimmunologic research is that a certain homogeneity is becoming evident. Researchers routinely examine global stress, depression, coping style, hardiness, social support, and so forth, without sufficiently developing specific models for the population or illness under consideration.

A consideration that will remain important in psychoimmunologic research concerns the role of behavioral factors in the mediation of apparent psychosocial influences on immunity. Poor eating habits, sleep deprivation, and increased use of psychotropic substances are all behaviors that may increase during stressful periods and may produce direct effects on the immune system (reviewed in Kiecolt-Glaser & Glaser, 1988). Physical exercise has also been shown to affect immune function, particularly NK cell activity (Brahmi, Thomas, Park, & Dowdeswell, 1985; Kanonchoff et al., 1984). It is therefore very important to assess these as objectively as possible in research.

Other pragmatic concerns in PNI research involve the immunologic aspects of the work. In general, research laboratories perform assays with less variability than do clinical ones. It is important that the technician performing the assay be blind to the hypotheses or experimental conditions of subjects because many aspects of immunologic assays involve fairly subjective judgements.

It is important that PNI researchers remain aware of the bidirectional nature of psychoimmunologic relationships, an aspect that has barely been touched upon here. This is particularly relevant, of course, in the interpretation of results from studies with correlational designs.

The development of effective psychosocial interventions for immune-related illness remains an important task for the future. The controlled intervention design, in which potentially valuable applications of psychoimmunologic research are tested, represents a scientifically superior method for revealing causal relationships between psychosocial and physiological processes.

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