Depression and Immunocompetence: A Review of the Literature

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Recent evidence suggests that there is a relationship between depression and immunity. On the basis of these studies, it has been argued that depressed mood may increase susceptibility to disease by means of aberrations occurring within the immune system. Empirical research investigating the relationship between depression and immunity is reviewed here. Studies examining both clinical and nonclinical manifestations of depression are discussed and evaluated. This review reveals that indexes of immunocompetence are lower among people exhibiting depressive symptomology and suggests that immune alterations may be more related to dysphoric mood than to specific situations or events. Alternative hypotheses accounting for links between depressed affect and altered immune states are provided, and suggestions for future research are offered.

The question of whether depression leads to changes in immune states warrants investigation, particularly in light of the large number of people who suffer from depression while sick with chronic illnesses and immune-related disorders such as acquired immunodeficiency syndrome (AIDS) and certain cancers. A competent immune system ensures health by providing protection against pathogenic processes and promotes healing and recovery from disease and injury. Immunologic disturbances may increase susceptibility to disease or prolong existing medical problems (Rosen, Cooper, & Wedgewood, 1984). Studies linking depression to changes in overall immunocompetence could provide clues concerning the role of affect in the etiology and course of disease states.

Depressed mood is a common experience, particularly for people who are sick or who have experienced a major loss or separation. Depression reaches clinical magnitude in nearly 10% of the population (Robins et al., 1984). A relationship between depression and immunocompetence might identify people who are at greater risk for health disturbances and target individuals who may have propensities for chronic health problems.

The purpose of this review is to examine empirical studies of depression and immunity to assess the nature of the relationship and identify conditions whereby associations between depression and altered immune states exist. This review draws from studies that assess immunocompetence in people diagnosed with a depressive disorder and in human and nonhuman primates experiencing the disruption of a significant attachment bond.

Measuring depression and immunocompetence is a complex issue. Depressive episodes, as well as immune responses, are not static events that are easily quantified. Depression occurs over a wide range of intensities and most likely represents a family of disturbances. A variety of immune processes exist as well, but all do not reflect equal events. Therefore, included in this review is a brief overview of definitional and conceptual issues regarding the assessment of depression and immunocompetence.

Depression: Conceptual and Definitional Issues

The term depression is a noted source of confusion in the literature, in part because of characterizations of depression as a mood state, a set of symptoms, and a clinical syndrome (Coyne, 1986). Broadly defined, depression is dysphoric mood marked by feelings of sadness, helplessness, worthlessness, loneliness, and often guilt. Weight loss, sleep disturbances, and crying spells are also signs of a depressive episode. Although these signs and symptoms have been well documented, a wide heterogeneity exists among depressed people. Differences in etiology and presentation of depressive symptoms are what commonly determine whether feelings are a normal response to an event or if they warrant the diagnosis of a clinical disorder.

Because depression has been conceptualized in such an array, there are a number of approaches for investigating the relationship between depression and immunocompetence. This review examines studies of patients diagnosed with a depressive disorder and includes studies of individuals who have experienced separation events. To determine whether there is a generalizable relationship between depression and immunocompetence and to investigate the possibility that certain features of depression account for this relationship, three basic questions are addressed. First, is there a link between depression and altered immunity? Second, if there is a relationship, does it occur for clinical as well as for nonclinical depressive episodes? Finally, the nature and direction of reported associations between dysphoric mood and immune states will be examined to evaluate whether a causal relationship exists between depression and altered immunity.

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Clinical Depression

In clinical depression, dysphoric mood is prominent and often quite severe, persisting for several weeks, months, or even years. Clinical diagnoses of depression are heterogeneous, and a variety of classification schemes for the depressive disorders have been proposed. For example, distinctions have been drawn between endogenous and nonendogenous depressions. Endogenous depressions are reportedly linked to internal, biological factors, nonendogenous depressions are linked to clearer external, precipitating events. Primary and secondary distinctions are drawn as well to delineate depressive conditions that arise from circumstances such as illness or drug therapy. These example classifications are based on etiological factors, whereas others are determined more by clinical course, as in the distinction between unipolar and bipolar affective disorders. Bipolar depression is characterized by episodes of mania (e.g., excessive elation, hyperactivity, agitation) alternating with depressive episodes; unipolar depression lacks periods of mania.

Semantic issues present challenges to depression researchers, yet a number of developments have allowed greater diagnostic precision and reliability. The Diagnostic and Statistical Manual of Mental Disorders (DSM–III–R; American Psychiatric Association, 1987) serves as the dominant diagnostic system currently available, classifying depression into two types: major affective disorders (including unipolar and bipolar disorders) and other affective disorders that are not severe enough to warrant a major affective diagnosis but are present intermittently or chronically for at least 2 years.

Most studies of depression and immunity have used older diagnostic criteria such as the research diagnostic criteria of Spitzer, Endicott, and Robins (1978), which recommends clinical depression be at least a 1-week-long mood disturbance accompanied by three or more additional symptoms. Other studies have relied on the criteria of Feighner et al. (1972), requiring four symptoms with at least a month-long mood disturbance. Regardless of diagnostic criteria, depressive symptomology is the key feature of the clinical syndrome. Therefore, studies of patients suffering from clinical depression offer the best approach to investigating the relationship between depression and immunocompetence.

Nonclinical Depression

The disruption of an attachment bond is a powerful stimulus for depressive symptomology in both humans and in animals. For example, divorced people are more likely to suffer from clinical depression than are people who have never been divorced (Blumenthal, 1967). A review of prospective studies of bereavement also suggests that both young and old people suffer from depressive symptoms during the first year (Clayton, 1979). The prevalence of depressive symptoms among the divorced or widowed allows investigators to focus on these events as a means to study depression (e.g., Paykel, 1982). Separation studies provide an opportunity to study depression as a normal mood state and allow investigations into the development of symptomology.

Nonhuman primates that are separated from their mothers or repeatedly from their peers also display behavioral signs of depression (e.g., Hinde, Spencer-Booth, & Bruce, 1966; Kaufman & Rosenblum, 1967; Suomi, Harlow, & Domek, 1970). Nonhuman primates often withdraw from their environment, exhibit slouched posture, and engage in self-clasping, rocking behavior after separation from conspecifics. Similar responses have been documented in human infants after maternal separation (Bowlby, 1960; Robertson & Robertson, 1971; Spitz, 1946). Therefore, animal models of depression often entail separation from significant conspecifics (e.g., Crawley, 1984; McKinney, 1974). Although animal models of depression allow greater control of behavioral and environmental factors, they are limited in that they do not allow direct assessment of certain depressive symptoms, particularly mood.

Other Models

Attempts to manipulate depressed mood have included the use of various drugs and learned helplessness training techniques. Symptoms of depression have been reported after treatment with catecholamine-depleting drugs such as reserpine (Goodwin & Bunney, 1971); other symptoms occur in animals after learned helplessness training (Overmier & Seligman, 1967; Seligman & Maier, 1967; Weiss et al., 1981). Problems exist with both of these models. Reserpine only induces depressive symptoms in about 10% of those taking the drug (Goodwin & Bunney, 1971), and the use of drugs to study depression assumes that depression has a biological origin (Whybrow, Akiskal, & McKinney, 1984).

Although drug studies allow researchers to address important mechanistic questions about depression's biological basis, this may also lend to confusion in studies collecting physiological data such as immune measures. Few studies have investigated the effects of antidepressant drugs or depression-precipitating drugs like reserpine on human immunity, yet there is evidence that these drugs alter immune responses in animals (Devoino & Ilyutenok, 1968; Devoino, Korovina, & Ilyutenok, 1968; Devoino & Yeliseyeva, 1971; Kvarstein & Stormorken, 1971). For these reasons, studies examining the effects of psychotropic agents on immune states are not reviewed here.

Learned helplessness describes escape-avoidance learning deficits found in animals after exposure to uncontrollable, aversive events (Overmier & Seligman, 1967; Seligman & Maier, 1967). This response to noncontingency was developed into a model of reactive depression because of similarities between behaviors associated with learned helplessness and depressive symptomology (Seligman, 1975). Commonalities between the two include learning deficits, slowed responding, and passivity (Miller, Rosellini, & Seligman, 1986). Although there are documented similarities between learned helplessness and certain symptoms of depression, controversy exists over the adequacy of learned helplessness as a model for depression. Stomach ulcers are characteristic of learned helplessness but do not typically occur in depression, suggesting distinct differences between the two. Learned helplessness studies have also been criticized for their failure to identify postulated cognitive deficits in humans (Costello, 1978). In light of these criticisms and of recent inconsistencies between animal and human studies examining the relationship between learned helplessness training and immunocompetence (e.g.,
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Laudenslager, Ryan, Drugan, Hyson, & Maier, 1983; Maier & Laudenslager, 1988; Weisse et al., 1990), the learned helplessness literature is not reviewed.

Immunocompetence: Conceptual and Definitional Issues

Immunocompetence refers to the ability of an organism's immune system to protect against pathogenic processes. Proper functioning of the immune system entails constant surveillance for antigens and rapid response against these foreign entities. Hence, disturbances in immune function may place individuals at greater risk for health problems (Rosen et al., 1984). The incidence and duration of infectious episodes can be directly related to immunocompetence; therefore, many argue that assessments of various immune states provide a useful construct for conceptualizing and operationalizing physical health status. Unfortunately, immunocompetence is not an easy construct to define or measure. This section is not intended to describe all potential measures available for assessing immunocompetence but to provide the reader with an overview of measures that have been used in studies of depression. For discussion of the clinical relevance of these tests, see Stites (1984a, 1984b).

The immune system functions through the coordinated actions of a variety of cells and cellular products. Cells of the immune system, collectively termed leukocytes, or white blood cells, are broadly divided into three main classes: lymphocytes, monocytes, and granulocytes (e.g., neutrophils, basophils, and eosinophils). Functional differences exist among these diverse classes of cells, and further distinctions are drawn among leukocyte subpopulations. For example, lymphocytes are subdivided into B cells, T-helper cells, T-suppressor cells, and natural killer cells. B cells produce antibodies, which are serum proteins (immunoglobulins) that provide an important defense against bacterial infections. T-helper cells stimulate immunologic activities; T-suppressor cells down-regulate immune responses. Studies examining T-suppressor cells identify them through a receptor that is also found on a subset of T cells that serves cytotoxic (cell-killing) function. Natural killer cells represent an additional class of cytotoxic cells that provide important antiviral and antitumor defenses. Because these various leukocytes perform many different processes, immune function is assessed using several approaches. A number of functional assays are available to measure cell responses. Leukocytes possess a variety of capabilities, including the ability to proliferate in response to antigens, to move toward the site of infection (chemotaxis), to engulf foreign pathogens (phagocytosis), to destroy through specific lytic activities as in tumoricidal activity (cytotoxicity), and to generate humoral regulatory or growth factors (e.g., antibodies, interferons, and interleukins) that aid in the destruction or neutralization of antigens. Not all cells are capable of all of these activities; thus, the assessment of distinct cell functions often requires select assays.

Although most immune assays are performed in vitro and attempt to assess the activities of cells independently from one another, there are in vivo tests that measure the coordinated actions of a variety of cell types. In vivo measures may provide more meaningful assessments of immunocompetence because they consider the system as a whole. Skin tests for delayed hypersensitivity and measures of antibody production after exposure to antigen, as in a vaccine, are examples of in vivo measures. An additional in vivo index of immune function involves monitoring graft-versus-host responses to determine how well an organism can reject nonhistocompatible tissue grafts.

Most studies of depression and immunity rely on proliferation or cytotoxicity assays. Lymphocytes are stimulated to divide in vitro using plant lectins (mitogens) such as phytohemagglutinin (PHA), concanavalin A (Con A), or pokeweed mitogen (PWM). In general, PHA and Con A stimulate T cell proliferation, and PWM stimulates T-dependent B cells (Daguillard, 1972; Stites, 1984b); however, lymphocyte responsiveness to these mitogens tends to be nonspecific and highly correlated. Lymphocytes may also be stimulated to divide in vitro using allogecnic lymphocytes from nonhistocompatible donors, as in a mixed lymphocyte reaction test. Both mitogens and "nonself" lymphocytes activate lymphocyte proliferation. Other immune cells such as natural killer cells and macrophages (mature monocytes) can be challenged with tumor cells in vitro to assess tumoricidal activity.

Some depression studies use quantitative measures and calculate numbers, percentages, or levels of immune cells or cell products instead of cell activities. A crude quantitative measure is the total white blood count. The white blood cell count represents the number of total leukocytes per cubic millimeter of blood. Normal values are extremely variable (e.g., 5,000–10,000 cells/mm³), and deviations from this norm are difficult to interpret, particularly without a differential analysis—a breakdown of the WBC into lymphocytes, monocytes, and granulocyte percentages. Additional techniques (e.g., flow cytometry) are available for more detailed calculations of leukocyte subpopulations.

Additional quantitative techniques include the assessment of antibody status. For example, elevations in autoantibodies often indicate autoimmune processes in which the immune system reacts against self antigens. On the other hand, elevations of specific antibodies to latent viruses such as herpes simplex virus or Epstein-Barr virus may indicate reactivation of the virus and, hence, suggest lowered immunocompetence (Glaser & Gottlieb-Stematsky, 1982). Common functional and quantitative assays of immunocompetence are summarized in the Appendix.

Clinical Depression and Immunocompetence

There is considerable evidence that altered immune states are present in individuals diagnosed with a depressive disorder. Reported most often is that depressed patients have lower lymphocyte responses to mitogens. For example, Kronfol, Silva, Greden, Dembinski, and Carroll (1982) measured lymphocyte responses to mitogens in 14 patients diagnosed as melancholic in accordance with RDC. When compared with 15 nonmelancholic psychiatric controls and 10 normal controls, these patients were found to have lower lymphocyte responses. In a follow-up study, Kronfol et al. (1983) examined lymphocyte responses to mitogens in 26 RDC-diagnosed patients and obtained similar results indicating lower responses in the depressed group. Although the severity of depressive symptoms was not directly correlated with lymphocyte responses, a trend
showing lower lymphocyte responses in the more severely depressed was revealed when subjects were divided into groups by high, moderate, and low Hamilton Rating Scale for Depression (HRSD) scores.

These findings of lower lymphocyte responsivity among depressed patients have been replicated in several studies of similar design (Calabrese et al., 1986; Darko, Lucas, & Gillin, 1986; Kronfol & House, 1984, 1989; Kronfol, House, Silva, Greden, & Carroll, 1986; Schleifer et al., 1984; Syvalatihi, Eskola, Ruuskanen, & Laine, 1985). All of these studies compared lymphocyte responses of depressed patients to those of normal controls, and although most studies used RDC for diagnostic purposes, others have yielded consistent findings using DSM-III criteria, offering strong support that clinical depression and reduced lymphocyte function go hand in hand.

Many depression studies have also included quantitative measures of immunocompetence, assessing numbers or percentages of lymphocytes. Depressed patients have been found to exhibit lower numbers and percentages of leukocytes (Kronfol & House, 1984; Krueger, Levy, Cathcart, Fox, & Black, 1984; Schleifer et al., 1984; Schleifer, Keller, Siris, Davis, & Stein, 1985; Targum, Marshall, Fischman, & Martin, 1989). Studies finding alterations in leukocyte numbers consistently report lymphopenia (decreased numbers of lymphocytes), neutrophilia (increased numbers of neutrophils), or elevated white blood cell counts.

Additional studies offer evidence that other aspects of immune function are altered during clinical depression as well, but only a few studies have included alternative measures of immunocompetence (e.g., natural killer cell activity, neutrophil activity, antibody production). Preliminary evidence suggests that natural killer cell activity is lower among the clinically depressed, particularly those patients with more severe symptomology. For example, Irwin and Gillin (1987) studied 11 patients who were hospitalized with major depressive illness and compared natural killer cell activity in these patients with activity levels among 7 controls. All patients were diagnosed in accordance with RDC and were drug free for at least 3 weeks before the study’s onset. Results indicated lower natural killer cell activity among the depressed patients. In addition, Hamilton depression scores were negatively correlated with natural killer cell activity, lending credence to the notion that dysphoric mood is associated with immune aberrations.

These findings of reduced natural killer activity in major depression have been recently confirmed by two additional studies (Mohl et al., 1987; Nerozzi et al., 1989) but are inconsistent with data from Schleifer, Keller, Bond, Cohen, & Stein (1989). Schleifer et al. (1989) report no differences in natural killer cell activity between depressed patients and controls. Because so few studies have assessed natural killer cell activity, inconsistencies in the literature are difficult to resolve. However, separation studies discussed later in this article suggest that natural killer cell activity is inversely related to depressive symptomology.

Another aspect of immune function that has been studied in depressed patients is neutrophil activity. In a prospective study, O’Neill and Leonard (1986) reported that neutrophil activity was lower among depressed patients than controls. Drug-free patients who were diagnosed with endogenous depression by DSM-III criteria were followed over a 6-week period during their treatment with mianserin, a serotonin antagonist. Neutrophil activity was assessed before their drug therapy and during 6 weeks of treatment. Before treatment, neutrophil activity was significantly lower among the depressed patients compared with controls. During the 6 weeks of treatment, 8 of the 9 patients studied were relieved of their depressive symptoms. As depression scores (HRSD) declined, neutrophil activity increased, and by the 3rd week of treatment, neutrophil activity of the depressed patients was no longer significantly lower than that of controls. Gottschalk, Welch, and Weiss (1983) also report lower neutrophil activity in depressed patients, but only 3 of 7 patients examined in their study exhibited neutrophil responses below those of controls. Neutrophil activity was assessed differently in these two studies making them difficult to compare; yet the data from O’Neill and Leonard (1986) suggest that neutrophil activity decreases during a depressive episode and that it increases as symptoms of depression subside.

One final aspect of immune function that has been studied in depressed patients is antibody production. To investigate how well depressed patients generate antibodies against cholera after vaccination, Friedman, Cohen, and Iker (1967) collected blood samples from 22 depressed patients, 10 schizophrenic patients, and 7 normal controls for 2 weeks after vaccination. Results revealed that the depressed were no different in their ability to generate an antibody response than were normal control subjects, suggesting that B cell function may not be altered in patients suffering from clinical depression.

Studies reviewed thus far suggest that a variety of immune processes may be reduced during clinical depression, but that reduced lymphocyte responsiveness is the most consistent immune aberration noted among the clinically depressed. However, some recent studies have reported normal lymphocyte function in depressed patients (Albrecht, Helderman, Schlesscr, & Rush, 1985; Althshuler, Plaeger-Marshall, Richter, Daniels, & Baxter, 1989; Darko et al., 1989; Schleifer, Keller, Bond, Cohen, & Stein, 1989; Schleifer, Keller, Siris, Davis, & Stein, 1985; Sengar, Waters, Dunne, & Bower, 1982). Close examination of these studies reveal patterns that offer insight into those conditions under which depressives may be more prone to exhibit reduced lymphoproliferation. For example, in studies that report normal lymphocyte function among the depressed, patients tended to be younger patients with milder depressive symptomology. In addition, patients exhibiting reduced lymphocyte function tend to be unipolar depressives. For example, Sengar et al. (1982) collected data exclusively from bipolar patients to determine whether these patients differed immunologically from their well siblings or from normal controls. Results revealed that there were no differences in lymphocyte function or in numbers of T and B cells between bipolar patients and either control group, suggesting that bipolar patients do not exhibit reduced immune function.

In a study examining lymphocyte function and T cell subpopulations in a sample of depressed patients that included both bipolar and unipolar, Albrecht et al. (1985) report comparable immune states between depressed patients and controls. Lower lymphocyte responses were reported among the patients, but only after the initiation of treatment with either tricyclic antidepressants or electroconvulsive therapy. Comparisons
were not drawn between the bipolar and unipolar patients nor were individual subject response values included, making it difficult to ascertain whether the unipolars exhibited lower lymphocyte responses than the bipolar. However, data from other studies suggest that unipolar patients exhibit lower lymphocyte function than bipolar.

For example, Altschuler et al. (1989) assessed lymphocyte function in a group of depressives that included both bipolar and unipolar patients. Results revealed a lack of differences between depressed patients and controls in lymphocyte responses to one dose of mitogen, and when a higher dose was used, depressed patients exhibited higher lymphocyte responses than controls. Average lymphocyte responses were slightly higher among the bipolar than the unipolars, suggesting the possibility that the higher lymphocyte response data of the bipolar offsets the lower average responses of the unipolars, washing out overall differences that may have been present between the depressed unipolar patients and controls. The data from this study supported the findings of Sengar et al. (1982) and of Albrecht et al. (1985) suggesting that bipolar do not exhibit reduced lymphocyte function.

Studies suggest that quantitative immune differences exist between bipolar and unipolar depressives as well. Reduced numbers of circulating lymphocytes appear to be more common among unipolar depressives than bipolar depressives (e.g., Murphy, Gardner, Greden, & Carroll, 1987), offering an explanation for why studies including bipolar have not reported immune differences between patients and controls (e.g., Albrecht et al., 1985; Sengar et al., 1982). In addition, Mohl et al. (1987) suggest the possibility that reduced natural killer cell activity occurs more often among bipolar. Therefore, differences in results across studies examining depression and immunocompetence may be explained, in part, by differences in the specific patient subtypes studied.

Hospitalization may be another important factor related to altered immunity among the clinically depressed. In one study, Albrecht et al. (1985) reported a lack of immune differences between depressed patients and controls, and two thirds of the patients studied were outpatients. In another study, Schleifer et al. (1985) collected immune data from ambulatory depressed patients, patients undergoing elective surgery, and schizophrenic patients to determine whether immune aberrations were a function of the depressive disorder, of hospitalization effects, or of the psychiatric disturbance in general. Although absolute numbers of T cells were lower in the depressed patients, no immune differences were noted among the groups. Ambulatory depressed patients did not exhibit lower lymphocyte responses. Because hospitalized schizophrenics and patients scheduled for elective surgery did not exhibit altered immune function, the authors concluded that reduced lymphocyte function among clinically depressed patients may be related to the severity of the depressive symptoms.

Recently, however, Schleifer et al. (1989) followed up this research in a larger study of 91 patients with unipolar depression and found support that hospitalization is related to reduced immune function among the depressed. Depressed patients and matched controls exhibited comparable lymphocyte responses, lymphocyte subsets, and natural killer cell activity. In addition, there was a significant interaction between age and hospitalization status with regard to lymphocyte function. Inpatients exhibited a decrease in mitogen responsiveness with increasing age, but outpatients showed no age-related changes (Schleifer et al., 1989). Schleifer et al. (1989) also reported age-related differences in lymphocyte responsiveness and in the number of T4 helper cells between the depressed patients and controls. Depressed patients did not exhibit increased lymphocyte responses or numbers of T4 cells with advancing age as did controls, suggesting that older depressives may be more likely to exhibit altered immunity than younger patients. Reports of reduced lymphocyte function among depressed patients is a common finding in studies that have included older patients or in studies in which patients were older than controls (e.g., Calabrese et al., 1986; Kronfol & House, 1989; Kronfol, House, Silva, Greden, & Carroll, 1986; Kronfol, Silva, Greden, Dembinski, & Carroll, 1982; Kronfol et al., 1983; Kronfol et al., 1982; Syvalahti et al., 1985). Studies comparing young, depressed patients with age-matched controls do not find differences in lymphocyte function (e.g., Altschuler et al., 1989). In addition, studies including quantitative measures suggest that altered leukocyte numbers among the depressed may be age-related as well (Murphy et al., 1987; Schleifer et al., 1989; Targum et al., 1989). All in all, these studies suggest that altered immunity among patients with major depressive disorder may be related to age, to diagnostic subtype, or to hospitalization status.

Summarized in Table 1 are studies that have investigated immune parameters among clinically depressed populations. These studies reveal that immune aberrations are present among the clinically depressed, particularly older patients diagnosed with a unipolar disorder severe enough to warrant hospitalization. Most widely cited is that lymphocyte responsivity is lower among depressed patients.

Data from studies examining leukocyte numbers suggest that some depressed patients exhibit quantitative immune disturbances, a finding that may also be more common among unipolars than bipolar. Reports of these aberrations have been generally consistent across studies (e.g., lymphopenia, neutrophilia, elevated white blood count). It is interesting that these leukocyte deviations are also noted in individuals receiving glucocorticoid treatments (Kehrl & Fauci, 1983; Slade & Hepburn, 1983). Studies reporting altered immune states among depressed patients have also noted elevated cortisol levels in these patients (Kronfol & House, 1984; Schleifer et al., 1985) or abnormal responses on the Dexamethasone Suppression Test (Targum et al., 1989). Other studies reporting quantitative changes in leukocytes did not assess cortisol. Clinical depression has been associated with elevated levels of plasma cortisol, at least in some patients (e.g., Carroll, 1982). It may be that a subtype of depressed patients who show higher levels of cortisol are also those same patients who exhibit alterations in leukocyte populations.

Studies of clinical depression include rigorous assessment of depressive symptomology, but some question whether dysphoric mood is responsible for the immune alterations noted in these studies. Clinical studies support a relationship between reduced immune function and the severity of depressive symptomology (e.g., Irwin & Gillin, 1987; Kronfol et al., 1983). However, drug histories, hospitalizations, confinement, and the like
<table>
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<tr>
<th>Study</th>
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<th>Depression measures</th>
<th>Immune measures</th>
<th>Results</th>
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<tr>
<td>Kronfol, Silva, Greden, Dembinski, and</td>
<td>Retrospective</td>
<td>14 melancholic patients, 15 nonmellancholic patients, 10 normal controls</td>
<td>RDC</td>
<td>LR to PHA, Con A, PWM</td>
<td>LR were lower in melancholic patients than in both nonmellancholic control groups</td>
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<td>Kronfol et al. (1983)</td>
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<td>HRSD</td>
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<td>Kronfol and House (1984)</td>
<td>Retrospective</td>
<td>13 depressed patients, 12 healthy controls</td>
<td>DSM-III</td>
<td>LR to PHA, Con A, PWM</td>
<td>LR were lower in depressed patients; responses did not correlate with depression scores, but a split of high, medium, and low scores revealed an inverse trend in LR</td>
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<td>Kronfol, House, Silva, Greden, &amp; Carroll (1986)</td>
<td></td>
<td>11 depressed patients with high urinary cortisol, 22 depressed patients with normal cortisol, 20 normal controls</td>
<td>RDC</td>
<td>LR to PHA, Con A, PWM</td>
<td>Both depressed groups had lower LR but weren't different from one another</td>
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<tr>
<td>Kronfol and House (1989)</td>
<td>Retrospective</td>
<td>40 depressed patients, 37 normal controls</td>
<td>DSM-III</td>
<td>LR to Con A and PWM</td>
<td>LR to Con A and PWM were lower in depressed patients; WBC and neutrophil percentages were higher but lymphocytes and monocytes were lower among depressed patients</td>
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<td>Schleifer et al. (1984)</td>
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<td>18 depressed patients, 18 sex/age matched controls</td>
<td>RDC</td>
<td>LR to PHA, Con A, PWM</td>
<td>Deposited patients had lower LR and numbers of T and B cells</td>
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<tr>
<td>Calabrese et al. (1986)</td>
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<td>10 depressed patients, 11 normal controls</td>
<td>HRSD</td>
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<td>Syvalahri, Eskola, Ruskakian, and Laine (1985)</td>
<td>Retrospective</td>
<td>18 depressed patients, 25 normal controls</td>
<td>DSM-III</td>
<td>LR to PHA, Con A, PWM</td>
<td>LR to PHA were lower among depressed patients</td>
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<td>Krueger, Levy, Cathcart, Fox, and Black (1984)</td>
<td>Retrospective</td>
<td>6 depressed patients, 21 normal controls</td>
<td>DSM-III</td>
<td>LR to PHA, Con A, PWM</td>
<td>Deposited patients had lower numbers of T cells, T-helper cells and helper/suppressor ratios; LR data were not reported</td>
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<td>Darko, Lucas, and Gillin (1986)</td>
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<td>5 depressed patients, 5 sex/age/race matched controls</td>
<td>SADS</td>
<td>LR to PHA, Con A, PWM</td>
<td>Deposited patients had lower LR to Con A</td>
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<td>Targum, Marshall, Fischman, and Martin (1989)</td>
<td>Retrospective</td>
<td>21 elderly depressed patients, 77 sex/age matched controls</td>
<td>DSM-III</td>
<td>WBC with differential; lymphocyte subpopulations</td>
<td>Deposited patients had lower % of total lymphocytes, T cells, and T-helper cells</td>
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<td>Schleifer, Keller, Siris, Davis, and Stein (1985)</td>
<td>Retrospective</td>
<td>15 ambulatory depressed patients, 15 matched controls, 16 hospitalized schizophrenic patients, 16 matched controls, 10 elective surgery patients, 10 matched controls</td>
<td>RDC</td>
<td>LR to PHA, Con A, PWM</td>
<td>Deposited patients had lower numbers of T cells than controls; no other differences were noted</td>
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<td>Darko et al. (1989)</td>
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<td>20 depressed patients, 20 sex/age/race matched controls</td>
<td>DSM-III</td>
<td>LR to PHA, Con A; IL-2 production</td>
<td>No differences in overall LR and IL-2 production were noted</td>
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<td>Sengar, Waters, Duane, and Boucher (1982)</td>
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<td>25 bipolar patients, 9 well siblings of bipolar patients, 13 normal controls</td>
<td>SADS-L</td>
<td>LR to PHA, Con A, PWM</td>
<td>No differences were noted</td>
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<td>Schleifer, Keller, Bond, Cohen, and Stein (1989)</td>
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<td>91 depressed patients, 91 sex/age matched controls</td>
<td>SADS</td>
<td>LR to PHA, Con A, PWM</td>
<td>No immune differences were noted between and controls; older patients had lower LR and % of T-helper cells than older controls</td>
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<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>Depression measures</th>
<th>Immune measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albrecht, Helderman, Schlessner, and Rush (1985)</td>
<td>Prospective</td>
<td>18 patients with endogenous depression 9 patients with nonendogenous depression 13 normal controls 8 depressed patients 8 sex/age matched controls</td>
<td>HRSD SADS-L RDC BSI</td>
<td>LR to PHA, Con A, PWM Lympohocyte subpopulations</td>
<td>Depressed patients did not differ from controls; nonendogenous depressives did not differ from endogenous; LR were lower in depressed patients after treatment with TCAs or ECT</td>
</tr>
<tr>
<td>Altheuser, Plagelhofer-Mannehall, Richeimer, Daniels, and Baxter (1989)</td>
<td>Retrospective</td>
<td></td>
<td>DSM-III HRSD</td>
<td>LR to PHA</td>
<td>Depressed patients had higher LR than controls</td>
</tr>
<tr>
<td>Friedman, Cohen, and Iker (1967)</td>
<td>Prospective</td>
<td>22 depressed patients 10 schizophrenic patients 7 normal controls 11 depressed patients 7 normal controls</td>
<td>Not reported</td>
<td>Ab titer to cholera vaccine</td>
<td>Ab generation was not different in depressed patients than in controls</td>
</tr>
<tr>
<td>Irwin and Gillin (1987)</td>
<td>Retrospective</td>
<td>10 depressed patients (6 unipolar, 4 bipolar) 10 sex matched controls 22 depressed patients 22 sex/age matched controls</td>
<td>RDC HRSD</td>
<td>NK activity</td>
<td>NK activity was lower in depressed patients; NK activity was negatively correlated with depression scores</td>
</tr>
<tr>
<td>Mohl et al. (1987)</td>
<td>Retrospective</td>
<td>10 depressed patients (6 unipolar, 4 bipolar) 10 sex matched controls 22 depressed patients 22 sex/age matched controls</td>
<td>RDC SADS-L</td>
<td>NK activity</td>
<td>NK activity was lower in depressed patients</td>
</tr>
<tr>
<td>Nerezi et al. (1989)</td>
<td>Retrospective</td>
<td>7 depressed patients 10 controls</td>
<td>DSM-III HRSD</td>
<td>NK activity</td>
<td>NK activity was lower in depressed patients</td>
</tr>
<tr>
<td>Gottschalk, Welch, and Weiss (1983)</td>
<td>Retrospective</td>
<td>9 depressed patients before/after treatment 26 normal controls</td>
<td>HRSD Gottschalk Depression Scale</td>
<td>Neutrophil activity</td>
<td>Only 3 of 7 depressed patients had lower neutrophil activity than controls</td>
</tr>
<tr>
<td>O'Neil and Leonard (1986)</td>
<td>Prospective</td>
<td></td>
<td>HRSD</td>
<td>Neutrophil activity before and after treatment with mianserin</td>
<td>Before treatment, depressed patients had lower neutrophil activity than controls; after treatment, depression scores declined, and neutrophil activity rose to control levels</td>
</tr>
</tbody>
</table>

Note: RDC = research diagnostic criteria, LR = lymphocyte responses, PHA = phytohemagglutinin, Con A = Concanavalin A, PWM = pokeweed mitogen, HRSD = Hamilton Rating Scale for Depression, DSM-III = Diagnostic and Statistical Manual of Mental Disorders, WBC = white blood cell count, IgG = immunoglobulin G, IgM = immunoglobulin M, IgA = immunoglobulin A, SADS = Schedule for Affective Disorders, SADS-L = Schedule for Affective Disorders (lifetime version), BDI = Beck Depression Inventory, Ab = antibody, IL-2 = interleukin 2, BSI = Brief Symptom Inventory, NK = natural killer cell, TCA = tricyclic antidepressant, ECT = electroconvulsive shock therapy.

may also be related to immune alterations exhibited by the depressed inpatients.

Hospitalization has been shown to be a stressful experience that may cause elevations in urinary and plasma corticosteroid levels (Mason, Sachar, Fishman, Hamburg, & Handlon, 1965). Depressed patients with poorer lymphocyte responses have reported greater stress (Kronfol & House, 1984) and have exhibited elevated plasma cortisol levels (Schleifer et al., 1984). Hospitalization in a psychiatric ward may be related to lower lymphocyte responses because it is stressful or because it interferes with normal sleep patterns, diet, or exercise. However, Schleifer et al. (1989) suggest that immune function may be lower among hospitalized patients because these patients suffer from more depressive symptomology.

Studies of nonclinical depression suggest that symptoms of depression are related to lower aspects of immune function in nonhospitalized, nonmedicated individuals as well. Because depressed mood is most often associated with separation events, studies examining immune process among human and nonhuman primates during separation are reviewed in the next section.

Separation and Immuneocompetence

Human Studies

Immunocompetence has been shown to be compromised after events such as marital separation and the death of a spouse. Furthermore, dysphoric mood has been shown to be inversely related to immune function, particularly natural killer cell activity and lymphocyte function, even in studies that do not report reduced immune function during separation. For example, Irwin, Daniels, Bloom, and Weiner (1986) examined natural killer cell activity in women who had been widowed for less than 6 months, women whose husbands were diagnosed with terminal lung cancer, and women whose husbands were healthy. Results revealed that natural killer cell activity of the widows was not different from that of the other two groups. However, natural killer activity was inversely related to symptoms of depression in this study as well as in follow-up research (Irwin, Daniels, Bloom, Smith, & Weiner, 1987; Irwin, Daniels, Smith, Bloom, & Weiner, 1987).

In a prospective study, Irwin, Daniels, Smith, et al. (1987)
assessed natural killer cell activity and depressive symptoms in a sample of women before and after the death of their husband. Results revealed that neither immune function nor symptoms of depression differed between the pre- and postbereavement time periods. Depression scores varied greatly among the women, indicating individual differences in response to the husband’s death. However, depressed mood was highly correlated with decreased natural killer cell activity. The data from this study and from Irwin et al. (1986) suggest that reduced natural killer cell activity is not related to separation, per se, but to depressed symptoms that accompany the separation event.

Depressive symptomology is related to immune alterations in individuals exposed to stressful life events as well. In a study of 117 subjects with variable amounts of life change stress, natural killer cell activity was found to be significantly lower in individuals with high depression scores but not in those with overall high life change scores (Locke et al., 1984). Similarly, Linn, Linn, and Jensen (1984) examined 49 men who had recently experienced a death or serious illness in their family and compared a variety of immune measures from these men to those of 49 control subjects who had not recently experienced a similar event. Lymphocyte responses to PHA were comparable between men who had recently experienced a stressful life event and control subjects. However, a split based on high and low depression scores from the Hopkins Symptom Checklist revealed that the more depressed subjects exhibited lower lymphocyte responses than the less depressed men. Thus, lymphocyte function was lower in subjects reporting depression, regardless of whether they had recently experienced a stressful event.

Additional studies have reported reduced aspects of immune function during separation without assessing the extent to which subjects were depressed. For example, Bartrop, Lazarus, Luckhurst, Kiloh, and Penny (1977) followed 26 persons immediately after the accidental or illness-related death of their spouse and compared immune data from these individuals with 26 controls. Six weeks after their spouse had died, widowed individuals exhibited lower lymphocyte responses than controls, but they did not differ from controls in T and B cell numbers, antibody titers, or autoantibodies or in delayed type hypersensitivity. Schleifer, Keller, Camerino, Thornton, and Stein (1983) reported similar findings in a study that measured lymphocyte function in 15 spouses of women who were terminally ill with breast cancer. Lymphocyte responses were tested before the death of the spouse, within 1 month after the death, and during a 4–14-month follow-up period. Results of this study revealed that lymphocyte responses were lower postbereavement than prebereavement, and a trend toward baseline was observed during the follow-up time period. Although this study and the study by Bartrop et al. (1977) suggest that lower lymphocyte responses are present during separation, the role of depression in directing the relationship between separation and lower immune function was not directly assessed, because measures of depression were not included in either study.

Some separation studies have assessed depressed mood and indexes of immune function but have not examined whether direct relationships exist between the two. For example, Kiecolt-Glaser et al. (1987) studied 38 women undergoing marital separation and compared a variety of immune measures from these women to measures from 38 married controls. Divorced/
Table 2 provides a summary of studies examining the relationship between separation and immunocompetence. Clearly, both retrospective and prospective data from human and animal studies suggest that separation is associated with decreased lymphocyte and natural killer cell function. Natural killer cell activity has been shown to be lower among individuals who are widowed (Irwin, Daniels, Smith, et al., 1987) as well as among those anticipating the death of a spouse (Irwin, Daniels, Risch, Bloom, & Weiner, 1988); however, there is evidence that lower immune function may be more directly related to how a person reacts to a distressing event. Although many studies did not examine direct relationships between depressed mood and parameters of immune function, those studies that did suggest that immune disturbances are associated more with dysphoric mood than with separation (e.g., Irwin et al., 1986; Irwin, Daniels, Bloom, et al., 1987).

Studies of nonhuman primates also suggest that being separated from a significant conspecific can result in lowered immune function. However, the extent to which immune changes were the result of depression is difficult to assess. Infant monkeys separated from their mother showed signs of agitation and exhibited slouched posture, but these behavioral markers were not consistent across all monkeys. For example, mothers of the infant primates did not show any behavioral changes that would indicate a depressive response, yet lymphocyte responses declined in these animals (Laudenslager et al., 1982). Dissociations between behavioral responses to separation and immune alterations are difficult to interpret, particularly in light of studies revealing that dissociations exist between behavioral and neuroendocrine signs of distress in primates (Levine, Johnson, & Gonzalez, 1985). In any event, these studies provide strong evidence overall that altered immune states occur in animals that experience separation from conspecifics, and previous research suggests that these studies offer a model for reactive depression (e.g., Hinde et al., 1966; Kaufman & Rosenblum, 1967; Suomi et al., 1970).

General Discussion and Conclusions

It is widely held that depression and immunocompetence are related. Nearly 40 studies investigating the relationship between depression and immunity have been published over the last decade and are reviewed here. Studies of people suffering from depressive disorders suggest that indexes of immunocompetence are lower among the clinically depressed, particularly older, hospitalized patients with unipolar disorder. Immune function may be lower among these patients because they suffer from more severe depressive symptomology. Severity of depressive symptoms have been related to lower immune function in both clinical (e.g., Irwin and Gillin, 1987; Kronfol et al., 1983; O’Neill & Leonard, 1986) and nonclinical populations (e.g., Irwin et al., 1986; Irwin, Daniels, Bloom, et al., 1987; Irwin, Daniels, Smith, et al., 1987; Linn et al., 1984), suggesting that immune aberrations are indeed related to dysphoric mood. Therefore, immune alterations may be more a function of the severity of depressive symptomology than of a specific situation or event.

Most studies have examined lymphocyte responses to mitogens, yet a few recent studies suggest that other immune measures, such as natural killer cell activity, may be compromised during depression. Although various immune indexes are difficult to compare across studies, they all suggest that an array of immune aberrations may be present during depressive episodes. Whether altered immune function is caused by depression, however, is more difficult to determine. Because depression is associated with behavioral changes that are capable of affecting immune processes, the mechanisms underlying this relationship are unknown, and causal inferences are tentative at best. Many changes occur during depression that could account for reduced immune function. Sleep patterns (Palmblad, Pettrini, Wasserman, & Akerstedt, 1979), nutritional status (Bisel, Edelman, Nauss, & Suskind, 1981; Worthington, 1974), exercise (Simon, 1984), alcohol use (VanHiel, 1983), and cigarette smoking (Holt & Keast, 1977) are all known to have effects on the ability of lymphocytes to proliferate in the presence of mitogens.

Another variable to consider in studies assessing immunocompetence among the bereaved, separated, divorced, and clinically depressed is stress. Depressive symptoms are associated with exposure to stressful events (Anisman & Zacharko, 1982; Garber, Miller, & Seaman, 1979), and studies that preclude the possibility that stressful life events are related to lowered immune function are difficult to design. Human stress studies consistently yield lower lymphocyte responses to mitogens after stressful events (for reviews see Jemmott & Locke, 1984; Locke, 1982). The relationship between stress and depression is complex. Some investigators argue that depression results from exposure to chronic or uncontrollable stresses; others argue that depression is a stressor (Anisman & Zacharko, 1982). The two can be highly related responses to traumatic events; therefore, it is difficult to determine whether one, both, or some additional factor is responsible for lower immune function among depressed people. Studies that included measures of stress also noted that stress scores were significantly higher among the depressed (Kronfol & House, 1984; Linn et al., 1984). Thus, one cannot rule out perceived stress as a potential contributing factor to immune alterations observed in these studies.

Considerations for Future Research

Depression frequently accompanies serious and chronic illnesses. Therefore, investigating the nature of the relationship between depression and immunocompetence is an important goal. It has been estimated that 32% of all hospitalized medically ill patients exhibit symptoms of depression (Cavanaugh, 1983). If depression can interfere with proper immune function, it may interfere with healing processes or host defenses against other potential health hazards. Therefore, psychiatric interventions might be indicated for people who have serious or chronic illnesses to avoid further compromise of health status.

Many studies are difficult to interpret because subjects were taking antidepressant drugs or were taking other psychotropic medications before being studied. Before their participation in studies, some patients were subjected to drug "wash-out" periods of about 2 weeks. The effects of these drugs during chronic administration or after acute cessation are not known, making it difficult to assess whether lowered lymphocyte re-
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<tbody>
<tr>
<td>Laudenslager, Capitanio, and Reite (1985)</td>
<td>Retrospective</td>
<td>4 monkeys with history of separation&lt;br&gt;5 control monkeys without history of separation</td>
<td>No measures included</td>
<td>LR to PHA, Con A, PWM</td>
<td>Adult monkeys with early separation histories had lower LR than controls</td>
</tr>
<tr>
<td>Reite, Harbeck, and Hoffman (1981)</td>
<td>Prospective</td>
<td>2 peer-separated monkeys</td>
<td>Behavioral assessments (posture, self-play, agitation)</td>
<td>LR to PHA, Con A, PWM</td>
<td>LR declined during separation and returned to baseline after reunion</td>
</tr>
<tr>
<td>Laudenslager, Reite, and Harbeck (1982)</td>
<td>Prospective</td>
<td>2 separated mother–infant monkey pairs</td>
<td>Behavioral assessments (posture, self-play, agitation)</td>
<td>LR to PHA, Con A, PWM</td>
<td>LR declined during separation and returned to baseline after reunion in 1 mother and in both infants</td>
</tr>
<tr>
<td>Coe, Rosenberg, Fischer, and Levine (1987)</td>
<td>Prospective</td>
<td>29 mother–infant pairs of squirrel monkeys&lt;br&gt;7 mother–infant pairs of control monkeys</td>
<td>No measures included</td>
<td>Ab generation to viral challenge</td>
<td>Infants who were separated, alone in an unfamiliar environment, had lower antibody levels compared with controls and with infants who were separated, alone in a familiar setting</td>
</tr>
<tr>
<td>Kiecolt-Glaser et al. (1987)</td>
<td>Retrospective</td>
<td>38 divorced/separated women&lt;br&gt;8 married control women</td>
<td>BSI</td>
<td>LR to PHA, Con A, PWM; % of NK, THelper and T Suppressor cells; helper/suppressor ratio; EBV titers</td>
<td>Divorced/separated women had lower LR to PHA, lower % of THelper and NK cells, and higher EBV titers</td>
</tr>
<tr>
<td>Kiecolt-Glaser et al. (1988)</td>
<td>Prospective</td>
<td>32 divorced/separated men&lt;br&gt;32 married control men</td>
<td>BSI</td>
<td>EBV/HSV Ab titers; helper/suppressor ratio</td>
<td>Divorced/separated men had higher EBV/HSV titers but did not differ in % or ratio of helper/suppressor cells</td>
</tr>
<tr>
<td>Linn et al. (1984)</td>
<td>Retrospective</td>
<td>49 men with recent family death/illness&lt;br&gt;49 control men without recent family death/illness</td>
<td>Hopkins Symptom Checklist</td>
<td>LR to PHA, Con A, PWM</td>
<td>LR were lower in men with high depression scores, independent of life events</td>
</tr>
<tr>
<td>Bartrop, Lazarus, Luckhurst, Kiloh, and Penny (1977)</td>
<td>Retrospective</td>
<td>26 people after death of spouse&lt;br&gt;26 sex/age/race matched controls</td>
<td>No measures included</td>
<td>LR to PHA and Con A; T/B cell numbers; IgG, IgM, IgA; autoantibodies; DTH</td>
<td>LR to PHA and Con A were lower in the bereaved at 6 weeks, but not at 1–3 weeks; no other changes were noted</td>
</tr>
<tr>
<td>Schleifer, Keller, Camerino, Thornton, and Stein (1983)</td>
<td>Prospective</td>
<td>15 men (wives with terminal breast cancer)</td>
<td>Self-reported rating scale</td>
<td>LR to PHA, Con A, PWM; T/B cell numbers and percentages</td>
<td>LR were lower postbereavement than prebereavement with a trend toward baseline at follow-up; no change was noted in T or B cell numbers</td>
</tr>
<tr>
<td>Locke et al. (1984)</td>
<td>Retrospective</td>
<td>117 subjects varying in degree of life change</td>
<td>Hopkins Symptom Checklist SRRS</td>
<td>NK activity</td>
<td>Depression scores were inversely related to NK activity; life change scores were unrelated to NK activity</td>
</tr>
<tr>
<td>Irwin, Daniels, Bloom, and Weiner (1986)</td>
<td>Retrospective</td>
<td>12 recent widows (6 months after death)&lt;br&gt;16 women (husbands with terminal cancer)&lt;br&gt;11 control women (healthy husbands)</td>
<td>General Health Questionnaire HRSD</td>
<td>NK activity</td>
<td>Bereavement was not related to NK activity; NK activity was inversely related to depression scores</td>
</tr>
<tr>
<td>Irwin, Daniels, Smith, et al. (1987)</td>
<td>Retrospective</td>
<td>10 recent widows (1–4 months after death)&lt;br&gt;8 control women (healthy husbands)&lt;br&gt;6 women before and after husband’s death</td>
<td>HRSD</td>
<td>NK activity; WBC with differential</td>
<td>Bereaved had higher depression scores and lower NK activity than controls</td>
</tr>
<tr>
<td></td>
<td>Prospective</td>
<td></td>
<td></td>
<td></td>
<td>Depressive symptoms were inversely related to NK activity; no change in NK activity or depression after death of spouse</td>
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<td>Study 2</td>
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Table 2 (continued)

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<tr>
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<tr>
<td>Irwin, Daniels, Bloom, et al. (1987)</td>
<td>Retrospective</td>
<td>37 women varying in degree of life change</td>
<td>SRRS HRSD</td>
<td>NK activity; % of T-helper and T-suppressor cells; T-helper/T-suppressor ratio</td>
<td>Depression scores were inversely related to NK activity and numbers of T-suppressor cells but positively related to T-helper/T-suppressor ratios. Bereaved and anticipatory bereaved women had lower NK activity than controls.</td>
</tr>
<tr>
<td>Irwin, Daniels, Risch, Bloom, and Weiner (1988)</td>
<td>Retrospective</td>
<td>9 recent widows (less than 6 months) 11 women (husbands with terminal cancer) 8 control women (healthy husbands)</td>
<td>None reported</td>
<td>NK activity</td>
<td></td>
</tr>
</tbody>
</table>

Note: LR = lymphocyte responses, PHA = phytohemagglutinin, Con A = Concanavalin A, PWM = pokeweed mitogen, Ab = antibody, BSI = Brief Symptom Inventory, NK = natural killer cell, EBV = Epstein-Barr virus, HSV = herpes simplex virus, IgG = immunoglobulin G, IgM = immunoglobulin M, IgA = immunoglobulin A, DTH, delayed-type hypersensitivity, SRRS = Social Readjustment Rating Scale, HRSD = Hamilton Rating Scale for Depression, WBC = white blood cell count.

Responses could be an artifact of the drug holiday. Antidepressive medications such as monoamine oxidase inhibitors, tricyclic antidepressants, and anxiolytics agents have been shown to alter human lymphocyte responses in vitro (Nahas, Desoize, & Leger, 1979). Although little is known about the effects of these drugs on other immune responses in humans, a number of responses (e.g., lymphocyte responsivity to mitogens, delayed-type hypersensitivity, graft-versus-host responses) are inhibited in animals that are administered antidepressant drugs (Audus & Gordon, 1982; Descotes, Tedone, & Eureaux, 1985; Fleischer & Bucher, 1972). Studies including placebo control groups will help eliminate confusion regarding drug effects, particularly in clinical studies.

In nonclinical studies of separation, depression should not be assumed to develop nonspecifically. Although these events have been shown to precipitate depressive episodes, responses to separations are mediated by cognitions, social support, coping resources, and a variety of other intervening factors. Separation does not always result in depression (e.g., Irwin, Daniels, Smith et al., 1987). Therefore, it is necessary to assess depressive symptomology in studies of separation to determine whether depressed affect is related to immune changes that are noted. A number of standard self-report inventories are available for assessing the severity and time course of depressive symptomology in clinical and nonclinical populations. Multiple assessments that include newer strategies such as facial coding may prove fruitful as well. Researchers have reported increases in depressive symptomology and altered immunity among people during separation without assessing direct relationships between depressed mood and immunocompetence (e.g., Kiecolt-Glaser et al., 1987; Kiecolt-Glaser et al., 1988). These studies do not allow clear conclusions to be drawn about the nature of the relationship between depression and immunity. Therefore, the extent to which depression contributes to altered immunity among individuals undergoing separation events needs to be further investigated.

The clinical relevance of alterations in immune measures needs to be further investigated as well. Inferences should not be made about susceptibility to diseases until the relationship between host susceptibility and immune aberrations are established. Only three studies reviewed here included assessments of physical health (Bartrop et al., 1977; Darko et al., 1989; Kiecolt-Glaser et al., 1988). Of these, only Kiecolt-Glaser et al. (1988) reported poorer health among those experiencing marital separation, and the relationship between health and symptoms of depression was not assessed. Because studies have not investigated direct relationships between depressive symptomology, immune status, and health outcomes, it is unknown whether depression compromises health by means of altered immunity. A strong relationship between immune changes and health is unlikely, because altered immunity does not guarantee illness (Jemmott & McClelland, 1989). Therefore, the extent to which statistical significance reflects clinical relevance needs to be further explored as well.

Although there is no perfect approach to the study of depression and immunocompetence, there are a number of ways researchers could narrow or eliminate alternative hypotheses clouding current theories. To allow clearer conclusions about depression and to exclude alternative hypotheses, prospective studies of depression are needed. It is possible that depression is a reaction to major life events but that immune processes are affected before the development of depressed mood. Prospectively assessing responses to separation events will elucidate the time frame with which mood and immune changes occur. Furthermore, studies that follow bipolar patients over time could address whether immune states are enhanced during mania, thus providing an alternative method of investigating the relationship between mood and immunity.

It is difficult to address causality and the directional nature of the relationship between depression and immunocompetence. Given evidence from animal studies of common pathways between the immune and nervous system (e.g., Blalock, Bost, & Smith, 1985) and of data suggesting that immune response can evoke changes in noradrenergic neurons (Bese-dovsky et al., 1983), it is possible that depression is a result of altered immunity rather than a cause. However, prospective studies suggest that conditions such as bereavement precede immunologic disturbances (e.g., Schleifer et al., 1983). A randomized intervention design that tests various treatments for their effects in alleviating depression and related immune dis-
turbances would address whether antidepressant therapies could “correct” affect-linked immune aberrations. Of particular interest would be immune studies of depressed patients undergoing cognitive therapy. Cognitive therapy has been shown to be as effective as pharmacotherapy (e.g., Dobson, 1989), and it does not interfere with immunologic processes as antidepressant drugs have been shown to do (e.g., Clink & Shaw, 1982).

Finally, when studying depressed populations, attempts should be made to delineate possible mechanisms underlying changes in immune states. Assessment of health-related behaviors such as cigarette smoking, alcohol consumption, exercise, sleep, and use of other medications will allow researchers to establish the extent to which these contribute to immune changes. It is possible that health-impairing behaviors contributed to the reduced natural killer cell activity in studies reporting differences between depressed patients and controls. For example, Nerozzi et al. (1989) did not exclude patients who were smokers, and smoking has been shown to be related to reduced natural killer cell activity (Hershey, Prendergast, & Edwards, 1983). Irwin and Gillin (1987) included patients with a history of alcoholism, a possible contributing factor to the reduced natural killer cell function noted among the depressives. Strict exclusion criteria and multivariate techniques that take into consideration these factors would allow for clearer conclusions about the nature of the relationship between depression and immunocompetence.

Of interest as well would be studies that identify neuroendocrine mediators involved in the relationship between depression and changes in immune processes. Although cortisol has been widely proposed as the key hormone responsible for immune disarray during depression, several recent studies challenge this claim (e.g., Altszuler et al., 1989; Irwin et al., 1988; Kronfol et al., 1986; Nerozzi et al., 1989; Schleifer et al., 1989), and new evidence has emerged implicating humoral factors such as prostaglandins and prolactin (Calabrese et al., 1986; Darko et al., 1989). Clearly, innovative approaches pursuing these leads will help uncover such mechanisms. Although questions remain regarding mechanisms and the nature of the relationship between depression and immunocompetence, the studies reviewed here offer a solid framework on which to build future research.

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cyte numbers in endogenous depression. *Psychological Medicine, 17*, 381–385.


Appendix

*Immunological Assays Used as Indexes of Immunocompetence*

Quantitative indexes of immune status
- White blood count
- Differential analysis (lymphocytes, monocytes, granulocytes)
- Enumeration of cell populations and subpopulations
  - Natural killer cells
  - B cells
  - T cells (e.g., T-helper cells, T-suppressor cells)
- Antibody titers

Qualitative indexes of immune function
- Lymphocyte proliferation (concanavalin A, phytohemagglutinin, pokeweed mitogen)
- Mixed lymphocyte response
- Chemotaxis
- Phagocytosis
- Natural killer cell activity
- Lymphokine/monokine production (e.g., interferons)
- Generation of specific antibodies
- Delayed type hypersensitivity
- Graft-versus-host response

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