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Depression and Immunity: A Meta-Analytic Review

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A meta-analysis indicated that clinical depression was associated with several large alterations in cellular immunity. Analyzing only methodologically sound studies, reliable immune alterations included lowered proliferative response of lymphocytes to mitogens (effect size *rs* = .24–.45), lowered natural killer cell activity (*r* = .28), and alterations in numbers of several white blood cell populations (*rs* = .11–.77). Immune alterations were greater in both older and hospitalized samples. There was also evidence of a linear relation between intensity of depressive affect and indicators of cellular immunity. Estimates of sample sizes needed to detect reliable effects for each immune outcome are provided. How neuroendocrine mechanisms or health practices might link depression to immunity is discussed, and design features needed to better understand these pathways are specified.

Considerable evidence suggests that depression places people at increased risk for physical morbidity and mortality (Elliot & Eisdorfer, 1982). Recent evidence suggests that these relations hold for diseases associated with the immune system (e.g., cancer; Linkins & Comstock, 1990; Persky, Kempthorne-Rawson, & Shekelle, 1987; Shekelle et al., 1981). Increased risk among depressed persons is thought to be attributable to intense affect triggering biological changes that make people more susceptible to physical diseases. Because the immune system is known to respond to changes in affect (Ader, Felten, & Cohen, 1991; Jemmott & Locke, 1984; Kemeny, Solomon, Morley, & Herbert, 1992; O'Leary, 1990), research has focused on immune alteration as a pathway through which depression might influence physical health.

The association between clinical depression and immunity has been reviewed in several articles (e.g., Calabrese, Kling, & Gold, 1987; Kiecolt-Glaser & Glaser, 1991; O'Leary, 1990; Stein, Miller, & Trestman, 1991; Weisse, 1992). Although the general consensus has been that depression is associated with altered immunity, the conclusions drawn from the two most comprehensive and up-to-date reviews are at odds with one another. Weisse (1992) concluded that "studies of people suffering from depressive disorders suggest that indexes of immunocompetence are lower among the clinically depressed" (p. 483). Weisse was referring primarily to lymphocyte responses to mitogens when she used the term *immunocompetence,* but she did not differentiate between the possible mitogens. She stated that decreased natural killer (NK) cell activity may also characterize depressed persons but that not enough evidence exists yet. In terms of enumerative parameters, Weisse was not clear about the direction of findings. She first stated that "depressed patients have been found to exhibit *lower* [italics added] numbers and percentages of leukocytes" (p. 478) and then stated that consistent findings show that depressed persons have increased numbers of white blood cells, increased numbers of neutrophils, and decreased numbers of lymphocytes. Stein et al. (1991), on the other hand, concluded that enumerative measures of immunity do not distinguish depressed from nondepressed individuals and that "no consistent or reproducible alterations of functional measures of lymphocytes" (p. 173) have been reported in clinically depressed patients. Stein et al. were referring to both proliferative responses to mitogens and NK cell activity when they used the term *functional measures.*

In an attempt to resolve these disparate positions, we used meta-analytic procedures (Glass, 1976; Rosenthal, 1984, 1991) to examine the literature on clinical depression and immunity. Our analyses included evaluations of all published studies, as well as separate analyses restricted to studies that met minimal methodological criteria. We found substantial evidence for a relation between depression and both enumerative and functional measures of immunity. We begin by providing a brief description of the immune assays used in the reviewed studies. This is followed by a description of our meta-analysis, an integration of the results, and a discussion of the physiological and behavioral mechanisms that provide plausible explanations for a link between depression and immunity. Finally, we discuss design issues that should be considered in future research on this topic.

The Immune System

The purpose of the immune system is to protect an individual from disease-causing micro-organisms and other harmful materials (Male, Champion, Cooke, & Owen, 1991; Stites &

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Terr, 1991). These foreign materials are called *antigens,* which is short for "antibody generators." The organs of the body where most cells of the immune system are located are the bone marrow, thymus, lymph nodes, spleen, tonsils, appendix, and Peyer's patches (clumps of immune tissue in the small intestines). Because there is no easy way to access cells from these organs, psychoimmunological work with humans is limited to immune processes that occur in circulating peripheral blood. Circulating blood transports immune components between the organs of the immune system and sites of inflammation. Moreover, components of the immune system that circulate in blood (e.g., some types of white blood cells and antibodies) survey for and combat invading antigens. Therefore, circulating peripheral blood plays a key role in inflammatory and immune processes.

Descriptions of the immune system that the naive reader will find helpful have been provided by O'Leary (1990) and Calabrese et al. (1987); descriptions for the more advanced reader have been provided by Male et al. (1991) and Stites and Terr (1991). We encourage readers to refer to these sources for background information, and in this article we provide only brief descriptions of the tests of immunity used in the studies included in the meta-analyses.

In the studies we reviewed, two kinds of immunological assays were used: enumerative and functional. The primary enumerative assay involved simply counting the numbers or percentages of different kinds of white blood cells in the peripheral blood. The blood encompasses a number of different kinds of white blood cells. These cells can be differentiated into neutrophils, monocytes, eosinophils, basophils, and lymphocytes. There are also several different types of lymphocytes, including NK, B, and T cells. T cells can be further differentiated into helper T cells, cytotoxic T cells, and suppressor T cells (the latter two are usually assessed together as suppressor/cytotoxic T cells). Different cell types have distinct markers on them, and there are laboratory techniques (e.g., flow cytometry) that can separate and count cells on the basis of these markers. Quantification of this type is important because (a) a certain number of each type of immune cell is needed in order for the body to respond adequately to antigenic challenge and (b) a balance of the different cell types is needed for optimal immune response. Interpreting this quantification is difficult for several reasons, however. First, the numbers of different cell types do not necessarily correlate with the functional capacity of the immune system. Second, a variety of different mechanisms may explain a change in the number of a specific cell type in peripheral blood (e.g., cell migration to or from the lymph nodes or spleen and the peripheral blood). Finally, the health consequences of small changes in the absolute numbers or percentages of lymphocytes in peripheral blood (which are normally seen in healthy subjects) have not been determined. Nonetheless, counting the numbers or percentages of white blood cells is a relatively easy assay and is frequently included in studies.

A second enumerative technique is to quantify the amount of antibody (Ab) in serum to herpesviruses (Glaser & Gotlieb-Stematsky, 1982; Kiecolt-Glaser & Glaser, 1987). Almost everyone has been exposed to the common herpesviruses. These viruses differ from most other known viruses in that after exposure, they are present in the body all the time, although often in latent states. Latent virus sometimes replicates, creating antigens the immune system sees. Antibody is produced in response, and the amount of Ab produced fluctuates in relation to the amount of virus produced. A higher level of Ab to a latent virus is interpreted as a poorer outcome because it indicates a higher level of virus replication. However, the specific mechanism responsible for increased viral replication and Ab production is not clear (Blythe & Hill, 1984; Rouse, 1984). It may be that increases in Ab levels reflect decreased cellular immune function and therefore inadequate control of the latent virus (Glaser & Kiecolt-Glaser, 1987; Kiecolt-Glaser & Glaser, 1987). Alternatively, the extent of viral replication that occurs when the virus is reactivated may temporarily overwhelm the cellular immune response. Either way, once the cellular immune response has regained more effective control over the virus, the Ab level decreases again. Several techniques exist for quantifying the amount of Ab, including indirect immunofluorescence and enzyme-linked immunoabsorbance (Kiecolt-Glaser et al., 1985; Kiecolt-Glaser et al., 1988). Two herpesviruses whose Ab levels were assessed in the reviewed studies were herpes simplex virus type 1 (HSV-1; responsible for cold sores) and cytomegalovirus (CMV; produces a mononucleosis syndrome).

The second approach to studying the human immune system involves testing the functional capacity of immune cells. There are a number of functional tests, but only two were used in the studies we reviewed: lymphocyte proliferative response and NK cell cytotoxic activity. They are in vitro assays; that is, the functions of the cells are studied outside the body in the laboratory. Lymphocytes are the focus of both of these assays, because these types of cells perform some of the most important immunological functions when the body is battling invading organisms. The first assay, lymphocyte proliferation, examines how effectively stimulated lymphocytes divide (i.e., proliferate). Lymphocytes are stimulated by incubating them with substances (called *mitogens*) capable of nonspecifically inducing T or B lymphocytes to divide. When lymphocytes are incubated with mitogens for several days, they proliferate. A radioactively labeled DNA precursor (a protein) is added to the culture of dividing cells. Each newly formed cell incorporates the isotope into its DNA, and one can quantify the amount of proliferation that occurs by counting the amount of radioactivity taken up by the lymphocytes. It is assumed that the more proliferation that occurs, the more effectively the cells are functioning. Commonly used mitogens include phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM), which preferentially stimulate T cells (PHA and Con A) and B cells (PWM). The proliferative responses to these mitogens, however, are usually highly correlated. Lymphocyte division in response to each of several different concentrations of mitogen is assessed in this assay, with the expectation that the higher the concentration, the greater the proliferation. There is no theoretical basis for expecting that depression–immunity relations might differ at different concentrations.

The purpose of the second functional assay, NK cell cytotoxic activity, is to determine how effective NK cells are in killing tumor cells. Immune cells are incubated with radioactively labeled tumor cells for several hours. After incubation, the amount of radioactivity that has been released from the tumor cells is determined. This reflects the number of tumor

cells that have been killed (lysed) by NK cells. In immunological terms, the immune cells are "effectors" (i.e., they effect the killing outcome), and the tumor cells are "targets" (i.e., they are the targets for the NK cells). This assay is typically performed at several effector-to-target cell ratios (e.g., 50 immune effector cells to 1 tumor target cell; common ratios are 5:1, 10:1, 25:1, 50:1, and 100:1). With higher ratios, more killing is expected to occur because there are more effector cells available for every tumor target cell. Again, there is no theoretical basis for expecting that depression–immunity relations might differ at different effector-to-target ratios. The results of the NK cell assay are often expressed as lytic units (LUs), defined as the number of effector cells required to kill a certain percentage of target cells (Pross, Baines, Rubin, Shragge, & Patterson, 1981). Expressing the outcome in LUs provides a quantification of NK activity that is independent of the particular effector-to-target ratios included in a study, making it possible to compare results across studies in which different ratios were used.

The Meta-Analysis

Meta-analysis is the "statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings" (Glass, 1976, p. 3). This differs from two more frequent approaches to review, the narrative review and vote counting. Narrative reviews consist of descriptions of or impressionistic summaries of study findings within a particular area of research. In contrast, vote counting is an attempt to quantify the summary statistics found in the literature by counting and adding the positive and negative results of individual studies. Conclusions are then drawn by a straightforward comparison of the tallies. Weisse (1992) took the narrative approach to review studies of depression and immunity, whereas Stein et al. (1991) used vote counting.

We undertook a meta-analysis to clarify the discrepant conclusions of Weisse (1992) and Stein et al. (1991) and to determine whether reliable associations exist between depression and specific immune parameters. As an approach to study synthesis, meta-analysis has several advantages over narrative review and vote counting. First, both narrative and vote-counting reviews rely (either directly or indirectly) on the significance of findings in single studies for the basis of their conclusions. The p value that determines whether a test is significant (.05) is arbitrary, and by taking into account only whether an effect is significant one loses important information regarding the strength of the association. Furthermore, tests with p values close to significance (e.g., .06) would be reported as a marginal effect or counted as no effect when it may have been that a methodological factor such as insufficient sample size influenced this outcome. Stein et al. (1991) correctly noted that methodological problems like sample size and comparison group composition pervade much of the depression–immunity literature. Thus, one question we addressed was whether we would find reliable associations between depression and immunity in the 35 studies we reviewed if we focused on the strength of effects.

Second, given the methodological problems in many of the studies, drawing conclusions on the basis of the results of poorly designed studies is of questionable value. One advantage of conducting a meta-analytic review is that studies can be coded according to specific criteria and then analyzed on the basis of those criteria. In the present review, we defined minimum criteria for methodological rigor, and studies that met these criteria were analyzed separately to determine associations between clinical depression and immunity in studies with better designs.

Third, we were interested in exploring whether age, diagnosis subtype, and hospitalization status would moderate depression–immunity associations. Weisse (1992) suggested that differences between clinically depressed and nondepressed individuals are most likely when the clinically depressed subjects are older inpatients diagnosed with unipolar depression. Stein et al. (1991) also argued that immune alterations may not be a biological correlate of depression but rather may be related to age and symptom severity (see also Schleifer, Keller, Bond, Cohen, & Stein, 1989). Therefore, we conducted analyses to explore whether age, diagnosis, and hospitalization status moderated the association between depression and the immune system.

Fourth, we were interested in determining whether the numbers and percentages of various types of white blood cells were similarly associated with depression. This was a concern because in previous reviews of the literature (including Weisse's, 1992, and Stein et al.'s, 1991), studies that assessed the numbers and the percentages of white blood cell types were collapsed, despite the fact that the number and the percentage of a type of cell mean slightly different things. For example, a decrease in the percentage of T cells in peripheral blood can reflect one of two things: a decrease in the number of T cells or an increase in the number of another type of white blood cell (ensuring that the percentage of T cells decreases). Therefore, we examined cell numbers and cell percentages separately to determine whether these two outcomes were similarly associated with depression.

A final issue was whether the associations between depression and immunity were similar when depression was operationally defined as depressed mood and when it was defined as clinical depression. Depressive symptomatology is the key feature of the clinical syndrome of depression (Weisse, 1992). It can be easily assessed through self-report measures, rather than the structured interviews required to assess clinical depression. In addition, studies of depressed mood afford the opportunity to examine mood variation and its relation to immunity in individuals who do not have a psychiatric diagnosis. Therefore, where the data were available, we analyzed the associations between depressed mood and immunity.

In sum, we addressed five issues: (a) whether reliable associations between depression and immunity existed when the strength, rather than significance, of the effect was taken into account; (b) whether conclusions remained the same when the database was narrowed on the basis of methodological criteria; (c) whether age, diagnosis subtype, and hospitalization status moderated the depression–immunity associations; (d) whether interpretations were similar for the numbers and percentages of different cell types; and (e) whether conclusions were similar when depressed mood was the focus rather than clinical depression.

Method

Selection of Studies for Inclusion

To identify studies for inclusion in the meta-analysis, we conducted a computerized search (Medline) and inspected the reference lists from existing reviews as well as the reference lists of the articles retrieved from the reviews. Key words used in the computer search included *depression, psychoimmunology,* and *psychoneuroimmunology;* however, the majority of the articles were retrieved through the reference lists of recent reviews. These searches were conducted in October 1991. We included only those English-language articles that had been published in peer-reviewed journals and reported data from independent samples. Because the samples overlapped with those used in other studies, 2 studies reported by Irwin and colleagues were not included in the review (Irwin, Daniels, Bloom, & Weiner, 1986; Irwin, Smith, & Gillin, 1987).

To be included in the clinical depression and immunity meta-analyses, each study had to meet three criteria: Diagnoses of clinical depression had been made on the basis of either Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978) or the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1980); a nondepressed comparison group had been included; and the immune outcome was shared by at least one other study. These criteria yielded a total of 35 studies assessing clinical depression and immunity (18 studies overlapped with those reviewed by Weisse, 1992, and 22 overlapped with those reviewed by Stein et al., 1991). A list of these studies is provided in the Appendix.

A study had to meet four minimum methodological requirements to be included in the meta-analysis of the methodologically sound research: (a) The age and gender of the depressed individuals and comparison group were indicated in the article; (b) either the depressed and comparison subjects were matched on age and gender, or these two factors had been statistically controlled; (c) the depressed group had been drug free at the time of immune assessment; and (d) the comparison group had been psychologically and physically healthy. Fourteen studies of the relation between clinical depression and various indicators of the immune system met these criteria (indicated by asterisks in the Appendix). To proceed in the most conservative fashion, we used only these methodologically restricted studies to examine the influence of age, diagnosis, and hospitalization status on the clinical depression–immunity associations (although the pattern of findings was essentially the same when the larger set of studies was used). To define older and younger samples for analyses, we performed a median split on mean sample age (i.e., combined patient and control samples). This resulted in samples from 7 studies being characterized as younger (mean ages ranged from 29.4 to 42.2 years) and samples from 7 studies being characterized as older (mean ages ranged from 43.5 to 71.3 years).

Of the 14 methodologically restricted studies, only 1 sample of patients included both unipolar and bipolar diagnoses. Therefore, when we investigated diagnosis subtype, this particular study was dropped from analyses. In terms of hospitalization status, of the 14 methodologically restricted studies, 10 used only inpatients, 2 used largely inpatients (i.e., 10 of 12 and 40 of 44 were inpatients), in 1 study approximately two thirds of the subjects were inpatients, and in 1 study only outpatients were examined. Given the overlap with respect to specific immune parameters, there were not sufficient studies to conduct outpatient analyses. We did, however, conduct inpatient analyses by dropping the latter 2 studies from the analyses.

For studies of depressed mood, the following two criteria were used: Participants had been physically healthy (e.g., not cancer patients or patients with acquired immune deficiency syndrome), and the immune outcome was shared by at least one other study. In the depressed-mood studies that fit these criteria, depressed mood had been assessed by one of the following self-report or clinician-rated measures: the Profile of Mood States (McNair, Lorr, & Droppleman, 1971), the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Hopkins Symptom Checklist (Derogatis, Lipman, Richels, Uhlenhuth, & Covi, 1974), the Minnesota Multiphasic Personality Inventory (Dahlstrom, Welsh, & Dahlstrom, 1972), and the Hamilton Depression Rating Scale (HRSD; Hamilton, 1960). Nine studies of depressed mood and immunity met these criteria; a list is provided in the Appendix.

Meta-Analytic Techniques

In the analyses, Pearson's product–moment correlation coefficient (r) was used as the effect size estimate. An effect size indicates the size of an association between two variables, disregarding sample size. Whenever possible, we calculated effect sizes from means and standard deviations provided in the article. If these data were not provided, we calculated effect sizes from the results of a statistical test (e.g., a t or F value).[1] Combined or mean effect sizes were computed as follows. We transformed each r into a Fisher's z coefficient, summed these zs, divided the sum by the number of studies, and transformed the resulting z back into an r (Rosenthal, 1984, 1991). Two effect sizes were computed in each analysis, one that took sample size into account (weighted mean effect size) and one that did not (unweighted mean effect size). The weighted mean effect size assigns more weight to studies with larger numbers of subjects. This is important because correlations become more stable as sample size increases, and effect sizes based on large sample sizes deviate less than those based on smaller samples from the population effect size. There is no consensus on how to determine whether an effect size differs significantly from zero. However, two relevant pieces of information are whether the confidence interval includes the value zero (based on the random-effects model; Rosenthal, 1991), while another is the size of the z statistic (based on a fixed-effects model).

One common criticism of meta-analysis is that an inherent bias exists in the studies selected for inclusion because studies with significant findings are more likely to be published than studies with nonsignificant findings. This bias is referred to as the *file drawer problem.* That is, it is assumed that an unknown number of studies with effect sizes of zero remain unpublished somewhere in file drawers. Rosenthal (1984) suggested calculating a "fail-safe N" to address this bias. The fail-safe N is the number of file drawer studies required before the combined effect size is no longer significantly different from zero (based on the z statistic). If the fail-safe N is relatively small, a file drawer problem might exist. Rosenthal (1991) provided a formula for computing the fail-safe N as well as a rule of thumb for determining whether the fail-safe N is small enough to suggest an inclusion bias.

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[1] The meta-analyses were conducted with software provided by Ralf Schwarzer. The algorithms used for calculating effect sizes from means and standard deviations or on the basis of t or F tests reported in the articles are standard formulas used to calculate the correlation between measures obtained from two independent samples. When working with means and standard deviations, there are three steps: (a) Calculate $g = (M_1 - M_2)/SD$, where g is an effect size estimate, M_1 is the mean of one group, M_2 is the mean of the other, and SD is the pooled standard deviation of both groups (Glass, 1976); (b) calculate $d = (1 - (3/4*N - 9))*g$, where d is an unbiased effect size estimator (Hedges & Olkin, 1985, showed that g has a small sample bias); and (c) calculate $r = d/\sqrt{(d^2 + 4)}$, where r is the effect size entered into the meta-analysis. When working with an F value, the square root of F is first taken, resulting in a t statistic. The formula that converts t to r is as follows: $r = \sqrt{[t^2/(t^2 + df)]}$.

Specifically, if the fail-safe N for the analysis is less than 5 times the number of included studies plus 10, a file drawer problem may be present. For example, if 7 studies are included in an analysis, and the fail-safe N is below 45, an inclusion bias might exist. In the present review, therefore, for each analysis that resulted in a reliable effect, we computed a fail-safe N.

One of the articles included in the meta-analysis failed to report means and standard deviations, the actual effect size, or the probability value obtained, but the authors indicated that the results were statistically significant with $p < .01$. In this case, we assumed the probability level to be .01 and made the initial transformation to r. This was a conservative approach because the actual effect size would most likely have been larger than the value that was used. The authors of another four articles failed to report means and standard deviations, the actual effect size, or the probability value obtained but stated that the results were not statistically significant. In these cases, we assumed the effect sizes were equivalent to a zero correlation, again a conservative approach. Seven studies included a comparison group and two depressed groups (e.g., dexamethasone suppressors and nonsuppressors,[2] endogenous and nonendogenous depression, and major depression and major depression with psychosis). Because in every case there was no immune difference between the two depressed groups, we combined the data for the depressed groups and computed an effect size that represented the difference between the depressed and comparison groups.

In most studies in which more than one concentration of mitogen or more than one effector-to-target ratio (in the NK activity assay) was used, the researchers analyzed the data using repeated measures analyses of variance. In these cases, we calculated effect sizes from the F value for the main effect. The authors of one article, however, provided only means for each of the serial concentrations (in the case of the proliferative responses to PHA and Con A), and the authors of two articles provided only means for each of the effector-to-target ratios (in the case of NK cell activity). Because the procedures of meta-analysis rest on the assumption of the independence of effect sizes (Rosenthal, 1984, 1991), we allowed each study to contribute only one effect size per immune outcome (although studies did contribute more than one effect size to the review if they had more than one immune outcome). In these three studies, then, we used the mean of the relevant effect sizes.

Functional parameters included as outcomes were lymphocyte proliferation in response to PHA, Con A, and PWM, and NK cell activity. Enumerative parameters included the T helper:T suppressor ratio, antibody titers to HSV-1 and CMV, and white blood cell types. The types of cells used as enumerative outcomes included total white blood cells, four kinds of white blood cells (neutrophils, eosinophils, monocytes, and lymphocytes), three kinds of lymphocytes (NK, B, and T cells), and two kinds of T cells (helper T cells and suppressor/cytotoxic T cells). For some parameters (i.e., white blood cells and total lymphocytes), only the numbers of cells were used, but for other parameters a combination of numbers and percentages of cells was used (this is specified in every case). What was meant by the percentage of cells differed depending on the particular cell type under consideration. For example, the percentage of T cells was the percentage of lymphocytes that were T cells, and the percentage of lymphocytes was the percentage of white blood cells that were lymphocytes. This distinction is also specified in every case.

Results

Tables 1–3 present the results of the meta-analyses. Each table specifies the number of studies in which the specific immune parameters were assessed, the total number of subjects across studies, the mean effect size, the 95% confidence interval, the corresponding z in a normal distribution (using two-tailed probabilities to indicate significance), the fail-safe N, and whether there was a file drawer problem associated with the effect. Because the unweighted and weighted analyses showed equivalent effects in almost every case, we report results from only the weighted analyses,[3] but we specify the instances in which we found different effects using the unweighted analysis. Interpreting the effect size is equivalent to interpreting a correlation; the range is −1– +1, with higher values indicating a stronger effect. Effect sizes are positive when depression was related to an increase in an immune parameter and negative when depression was related to a decrease. When a file drawer problem is indicated, it is probably best to think of it as reflecting a marginal effect that needs further confirmation.

Meta-Analysis of Functional Measures of Immunity

Table 1 presents the results of the meta-analysis that addressed three issues regarding the functional measures of immunity: whether reliable associations between depression and immunity existed; whether the conclusions remained the same when the database was narrowed to methodologically sound studies; and whether age, diagnosis subtype, and hospitalization status moderated the depression–immunity associations.

Strength of association. Of the 35 studies in which clinical depression and functional indicators of immunity were assessed, the proliferative response to PHA was examined in 19, the proliferative response to Con A was examined in 17, the proliferative response to PWM was examined in 14, and NK cell activity was examined in 8. As the data show, across these studies clinically depressed subjects showed reliably less lymphocyte proliferation in response to PHA (−.300), Con A (−.415), and PWM (−.476), as well as lower NK cell activity (−.266), than did comparison groups.

Methodologically restricted studies. As Table 1 indicates ("Restricted studies"), when the four methodological criteria were imposed, depressed individuals again showed reliably less proliferation in response to PHA (−.243), Con A (−.361), and PWM (−.448), as well as lower NK cell activity (−.254), than did comparison subjects. When we compared these effect sizes with those from the larger set of studies by testing for differences between correlations, we found no differences in effect sizes.

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[2] Dexamethasone is a drug that functions physiologically as cortisol. In the dexamethasone suppression test, the patient is given dexamethasone, which should decrease the amount of cortisol the body produces. In some patients (dexamethasone suppressors) a decrease in cortisol occurs, whereas in others it does not (dexamethasone nonsuppressors). Nonsuppression represents an abnormal resistance to cortisol-induced negative feedback.

[3] To calculate the 95% confidence interval for the weighted analysis, the software provided by Schwarzer calculates the sampling error variance (which takes into account the weighted mean effect size; Hunter, Schmidt, & Jackson, 1982) and then the residual variance (obtained by subtracting the sampling error variance from the observed variance). Taking the square root of the residual variance results in the residual standard deviation. The residual standard deviation serves as the multiplier in the formula for the confidence interval. It follows that when the observed variance is totally explained by sampling error, the confidence interval becomes zero.

Table 1
Meta-Analysis of Functional Parameters From Clinical Depression–Immunity Studies

Immune parameter	No. of studies	*N*	Mean effect size (*r*)	95% confidence interval	*Z*	Fail-safe *N*	File drawer issue?
Phytohemagglutinin							
All studies	19	854	−.300	−.36 - −.24	9.44**	609	No
Restricted studies	8	397	−.243	−.34 - −.15	4.90**	63	No
Older samples	4	133	−.634	−.73 - −.52	8.20**	95	No
Younger samples	4	264	.005	−.12 - .13	.08	—	—
Unipolar depression	7	381	−.278	−.37 - −.18	5.51**	72	No
Hospitalized patients	6	185	−.448	−.56 - −.32	6.40**	85	No
Concanavalin A							
All studies	17	778	−.415	−.47 - −.36	12.89**	1,029	No
Restricted studies	7	382	−.361	−.45 - −.27	7.28**	130	No
Older samples	3	112	−.664	−.76 - −.54	7.97**	67	No
Younger samples	4	270	−.201	−.31 - −.08	3.32**	12	Yes
Hospitalized patients	5	170	−.602	−.69 - −.49	8.68**	134	No
Pokeweed mitogen							
All studies	14	690	−.476	−.53 - −.41	13.29**	899	No
Restricted studies	4	294	−.448	−.54 - −.35	8.08**	93	No
Older samples	2	82	−.869	−.91 - −.80	10.57**	81	No
Younger samples	2	212	−.154	−.28 - −.02	2.24*	2	Yes
Hospitalized patients	2	82	−.869	−.91 - −.80	10.57**	81	No
Natural killer cell activity							
All studies	8	514	−.266	−.35 - −.18	6.13**	103	No
Restricted studies	6	438	−.254	−.34 - −.16	5.39**	58	No
Older samples	2	112	−.392	−.54 - −.22	4.28**	12	Yes
Younger samples	4	326	−.204	−.31 - −.10	3.70**	16	Yes

Note. Older, younger, unipolar, and hospitalized analyses include only studies from the methodologically restricted set of studies. Dashes indicate that values are not applicable.
* $p < .01$. ** $p < .001$ (two-tailed).

Age, diagnosis, and hospitalization status. Regarding the moderating effect of age on depression–immunity associations, Table 1 shows the results of analyses conducted separately for older samples (ages 43.5–71.3 years) and younger samples (ages 29.4–42.2 years) for each of the functional parameters. Testing for differences between correlations, we found the strength of the effect for older clinically depressed subjects to be reliably stronger than that for younger subjects in each case, including the proliferative response to PHA (−.634 vs. .005), Con A (−.664 vs. −.201), and PWM (−.869 vs. −.154; all $ps < .001$), as well as for NK cell activity (−.392 vs. −.204, $p < .05$). Although the effect sizes for three of the four functional parameters were statistically reliable in younger samples (unweighted analysis also showed a reliable effect for the fourth), an insufficient number of studies resulted in the effects' being vulnerable to the file drawer problem. Finally, including only the older subjects in the analyses significantly increased the effect sizes over those found using the larger set of methodologically restricted studies (for proliferative responses, all $ps < .001$; for NK cell activity, $p < .01$).

Diagnosis subtype could be examined only in the context of the proliferative response to PHA. When the study was dropped that included patients with bipolar diagnoses, the effect size was −.278. This effect size was not different from that found for the larger set of methodologically restricted studies (−.243; $p > .10$).

The effect of hospitalization status was examined for the proliferative responses to all three mitogens but could not be examined for NK cell activity. Including only inpatients in these analyses reliably increased the effect sizes over those found using the larger set of methodologically restricted studies in each case, including the proliferative response to PHA (−.448 vs. −.243), Con A (−.602 vs. −.361), and PWM (−.869 vs. −.448; all $ps < .001$). These effects were similar to those seen when data from older subjects were used in the analyses. In the case of the proliferative response to PHA and Con A, the similarity was due to the fact that the set of studies that used hospitalized subjects was the same set that used older samples, but with two additional studies. In the case of the proliferative response to PWM, the same two studies were used in both the age and hospitalization analyses.

Meta-Analysis of Enumerative Measures of Immunity

Table 2 presents the results of the meta-analysis that addressed four issues regarding enumerative measures of immunity: whether reliable associations between depression and immunity existed, whether conclusions remained the same when the database was narrowed to methodologically sound studies; whether age and hospitalization status moderated the depression–immunity associations, and whether interpretations were similar for the numbers and percentages of different cell types.

Strength of association. As the data in Table 2 show, across all of the studies we reviewed, clinically depressed subjects had

Table 2
Meta-Analysis of Enumerative Parameters From Clinical Depression–Immunity Studies

Immune parameter	No. of studies	*N*	Mean effect size (*r*)	95% confidence interval	*Z*	Fail-safe *N*	File drawer issue?
White blood cells							
All studies	9	531	.205	.12 - .29	4.77***	67	No
Restricted studies	3	238	.381	.26 - .49	6.07***	38	No
Neutrophils							
All studies	5	425	.632	.57 - .69	14.68***	394	No
Restricted studies	3	238	.803	.75 - .84	15.62***	267	No
Monocytes							
All studies	3	217	.055	.08 - .19	0.80	—	—
Restricted studies	2	140	.263	.10 - .41	3.14***	5	Yes
Total lymphocytes							
All studies	11	748	−.117	−.19 - −.04	3.21***	31	Yes
Restricted studies	6	486	−.138	−.26 - −.05	3.05**	15	Yes
Older samples	3	202	−.268	−.39 - −.13	3.86***	14	Yes
Younger samples	3	284	−.042	−.16 - .08	0.71	—	—
Hospitalized patients	4	274	−.127	−.24 - −.01	2.11*	3	Yes
B cells							
All studies	12	631	−.030	−.11 - .05	0.74	—	—
Restricted studies	6	404	−.196	−.29 - −.10	3.97***	29	Yes
Older samples	3	156	−.473	−.59 - −.34	6.24***	40	No
Younger samples	3	248	<.001	−.13 - .13	0.01	—	—
Hospitalized patients	4	192	−.395	−.51 - −.27	5.67***	44	No
Numbers of cells	4	346	−.292	−.39 - −.19	5.54***	41	No
%s of cells	5	306	−.015	−.13 - .10	0.26	—	—
Total T cells							
All studies	13	652	−.347	−.41 - −.28	9.13***	387	No
Restricted studies	6	404	−.428	−.51 - −.34	9.01***	174	No
Older samples	3	156	−.776	−.83 - −.70	11.90***	154	No
Younger samples	3	248	−.094	−.22 - .03	1.47	—	—
Hospitalized patients	4	192	−.471	−.76 - −.60	10.99***	175	No
Numbers of cells	4	346	−.547	−.62 - −.47	11.06***	177	No
%s of cells	5	306	−.020	−.13 - .09	0.35	—	—
Helper T cells							
All studies	11	581	−.321	−.39 - −.24	7.94***	244	No
Restricted studies	4	337	−.355	−.45 - −.26	6.72***	63	No
Older samples	2	120	−.785	−.85 - −.70	10.62***	81	No
Younger samples	2	217	−.009	−.13 - .14	.13	—	—
Hospitalized patients	3	155	−.675	−.75 - −.58	9.63***	100	No
Numbers of cells	2	280	−.448	−.54 - −.35	7.89***	44	No
%s of cells	2	57	.173	−.10 - .42	1.29	—	—
Suppressor/cytotoxic T cells							
All studies	10	561	−.164	−.24 - −.08	3.89***	46	Yes
Restricted studies	4	338	−.143	−.25 - −.04	2.63**	6	Yes
Older samples	2	120	−.501	−.63 - −.35	5.82***	23	No
Younger samples	2	218	.080	−.05 - .21	1.17	—	—
Hospitalized patients	3	156	−.400	−.53 - −.26	5.17***	27	Yes
Numbers of cells	2	280	−.137	−.25 - −.02	2.30**	2	Yes
%s of cells	2	58	−.169	−.42 - .10	1.27	—	—
Large granular lymphocytes							
All studies	3	128	−.437	−.57 - −.28	5.15***	26	No
Natural killer cells							
All studies	4	154	−.280	−.42 - −.12	3.52***	14	Yes
Restricted studies	3	133	−.205	−.37 - −.03	2.36**	3	Yes
Helper:suppressor T cell ratio							
All studies	8	498	−.204	−.29 - −.12	4.59***	54	No
Restricted studies	3	302	−.379	−.47 - −.28	6.81***	48	No
Hospitalized patients	2	120	−.761	−.83 - −.67	10.09***	73	No
Antibody titers to herpes simplex virus type 1							
All studies	5	398	.557	.48 - .62	12.13***	266	No
Antibody titers to cytomegalovirus							
All studies	2	95	.694	.57 - .79	7.80***	43	No

Note. Older, younger, hospitalized, cell number, and cell percentage analyses include only studies from the methodologically restricted set of studies. Dashes indicate that values are not applicable.
* $p < .05$. ** $p < .01$. *** $p < .001$ (two-tailed).

a higher number of white blood cells (.205) and a higher number or percentage of white blood cells that were neutrophils (.632) than did comparison subjects. Depressed subjects also had a lower number of lymphocytes (−.117) and a lower number or percentage of lymphocytes that were T cells (−.347), helper T cells (−.321), suppressor/cytotoxic T cells (−.164), NK cells (−.280), and large granular lymphocytes (−.437; NK cells are a subset of large granular lymphocytes) than did controls. A decreased helper:suppressor ratio is also associated with depression (−.204), although this effect was not reliable when an unweighted analysis was used. Finally, depression was associated with increased antibody titers to HSV-1 (.557) and CMV (.694). Of these parameters, only the number of lymphocytes and the number or percentage of lymphocytes that were suppressor/cytotoxic T cells and NK cells were vulnerable to the file drawer problem. No differences between clinically depressed and nondepressed individuals were seen in the number or percentage of white blood cells that were monocytes or the number or percentage of lymphocytes that were B cells.

Methodologically restricted studies. When the studies included in the analyses were restricted by the four methodologic criteria, reliable differences between the clinically depressed and nondepressed subjects existed on every enumerative parameter tested. Depressed subjects had higher numbers of white blood cells (.381) and monocytes (.263), as well as higher numbers or percentages of white blood cells that were neutrophils (.803), than did comparison subjects. Depression was negatively related to the number of lymphocytes (−.138), and the numbers or percentages of lymphocytes that were B cells (−.196), T cells (−.428), helper T cells (−.355), and suppressor/cytotoxic T cells (−.143) and the percentage of lymphocytes that were NK cells (−.205). However, an unweighted analysis of the percentage of lymphocytes that were NK cells did not show a reliable effect. Again, depression was associated with a decrease in the helper:suppressor ratio (−.379). When we required that the studies included in the analysis meet some minimum methodological criteria, we found reliably larger effects for the number of white blood cells (.381 vs. .205) and monocytes (.263 vs. .055), the number or percentage of white blood cells that were neutrophils (.803 vs. .632), the number or percentage of lymphocytes that were B cells (−.196 vs. −.030) or T cells (−.428 vs. −.347), and the helper:suppressor ratio (−.379 vs. −.204; all $ps < .01$). Five enumerative parameters, however, remained vulnerable to the file drawer problem: the number of monocytes; the number of lymphocytes; and the number or percentage of lymphocytes that were B cells, suppressor/cytotoxic T cells, and NK cells.

Age, diagnosis, and hospitalization status. Regarding the moderating effect of age on depression–immunity associations, Table 2 shows the results of analyses conducted separately for older (ages 43.5–71.3 years) and younger (ages 29.4–42.2 years) samples for five enumerative parameters: total number of lymphocytes and the number or percentage of lymphocytes that were B cells, T cells, helper T cells, and suppressor/cytotoxic T cells. In each case, the effect in older clinically depressed subjects was significantly stronger than the effect in younger subjects, including the total number of lymphocytes (−.268 vs. −.042) and the number or percentage of lymphocytes that were B cells (−.473 vs. < .001), T cells (−.776 vs. −.094), helper T cells (−.785 vs. −.009), and suppressor/cytotoxic T cells (−.501 vs. .080). The weighted analyses showed none of the effect sizes to be statistically reliable in younger samples, but the unweighted analyses showed reliable effects for both the total number of lymphocytes and the number or percentage of lymphocytes that were T cells. Of all the reliable effects found for older samples, only the total number of lymphocytes was vulnerable to the file drawer problem. Including only the older subjects in the analyses reliably increased the effect sizes over those found using the larger set of methodologically restricted studies for four of the five enumerative parameters: the number or percentage of lymphocytes that were B cells (−.473 vs. −.196), T cells (−.776 vs. −.428), helper T cells (−.785 vs. −.355), and suppressor/cytotoxic T cells (−.501 vs. −.143; all $ps < .001$). The only parameter not significantly affected by restriction to older samples was the total number of lymphocytes, which increased only marginally (−.268 vs. −.138, $p < .10$).

Diagnosis subtype could not be examined in the context of any enumerative measure; however, the effect of hospitalization was examined for six enumerative parameters: total number of lymphocytes; the number or percentage of lymphocytes that were B cells, T cells, helper T cells, and suppressor/cytotoxic T cells; and the helper:suppressor ratio. Effect sizes for the total number of lymphocytes and the number or percentage of lymphocytes that were T cells were not reliably different when outpatients were eliminated from the analyses (all $ps > .05$). Including only inpatients in the analyses, however, reliably increased the effect sizes over those found using the larger set of methodologically restricted studies for the number or percentage of lymphocytes that were B cells (−.395 vs. −.196), helper T cells (−.675 vs. −.355), and suppressor/cytotoxic T cells (−.400 vs. −.143), as well as the helper:suppressor ratio (−.761 vs. −.379; all $ps < .001$). These effects were similar, however, to those seen when data from older subjects were used in the analyses. In the case of the helper:suppressor ratio, the same two studies were used in both the age and hospitalization analyses. For the remaining enumerative parameters, the set of studies that used hospitalized subjects was the same set of studies that used older samples, but with one additional study. Only the number or percentage of lymphocytes that were suppressor/cytotoxic T cells was not resistant to the file drawer problem.

Numbers and percentages of cell types. Again, only studies restricted by the methodological criteria were included in these analyses. Because there was an insufficient number of articles that reported either the number or percentage of different kinds of white blood cells, only four cell types were included in these analyses (B, T, helper T, and suppressor/cytotoxic T cells). In every case, there was a reliable effect for depression when the number of cells was used as the outcome. There were no reliable relations between depression and the percentage of any of the cell populations. Reliably stronger effects of depression emerged when the percentage outcomes were eliminated from the analysis for B cells (−.292 vs. −.196), T cells (−.547 vs. −.428), and helper T cells (−.448 vs. −.355; all $ps < .05$); the effect was of the same magnitude for suppressor/cytotoxic T cells (−.137 vs. −.143, $p > .10$). Of the four reliable effect sizes, only the number or percentage of lymphocytes that were suppressor/cytotoxic T cells was not resistant to the file drawer problem.

Table 3
Meta-Analysis of Continuous Associations Between Depression and Immunity

Outcome measure	No. of studies	*N*	Mean effect size (*r*)	95% confidence interval	*Z*	Fail-safe *N*	File drawer issue?
Depressed mood							
Phytohemagglutinin	3	259	−.131	−.25 - −.01	2.11*	2	Yes
Concanavalin A	3	259	.068	−.06 - .19	1.08	—	—
Natural killer cell activity	7	386	−.182	−.28 - −.08	3.58***	26	Yes
Severity of clinical depression							
Phytohemagglutinin	3	116	−.166	−.34 - .02	1.78*	1	Yes
Concanavalin A	2	108	−.272	−.44 - −.08	2.85**	4	Yes
Natural killer cell activity	5	247	−.103	−.23 - .02	1.62	—	—

Note. Dashes indicate that values are not applicable.
* $p < .05$. ** $p < .01$. *** $p < .001$ (two-tailed).

Meta-Analysis of Depressed Mood and Immunity

Table 3 presents the results of the meta-analysis that addressed whether similar conclusions resulted from analyses of studies of the depressed-mood–and–immunity relation in nondepressed samples as from analyses of studies of the clinical depression–immunity relation.[4] As is evident from Table 3, most immune parameters have not been studied in this context, and helper T cells, suppressor/cytotoxic T cells, the helper:suppressor ratio, and the proliferative response to PWM have each been quantified only once. Thus, these analyses focused on only three functional outcomes. Depressed mood was reliably associated with a decreased proliferative response to PHA (−.131) and decreased NK cell activity (−.182) but was not related to the proliferative response to Con A. Unweighted analyses did not show a reliable effect for the proliferative response to PHA.

To determine whether the linear relation between depressed affect and immune function found in studies of nondepressed subjects was found in studies of clinically depressed subjects, we conducted a further set of meta-analyses. Studies included in these analyses met our criteria for methodological soundness, assessed the proliferative response to PHA or Con A or assessed NK cell activity (i.e., one of the functional parameters used in the depressed-mood analyses), and used the HRSD (Hamilton, 1960) as a continuous measure of severity of depression. The HRSD is the standard clinician rating scale for assessing the severity of depression in the context of a depressive disorder (Rabkin & Klein, 1987). Consistent with the depressed-mood analyses, the data at the bottom of Table 3 indicate that severity of depression was reliably associated with a lower proliferative response to PHA (−.166). In contrast to the depressed-mood analyses, severity of depression was also reliably associated with the proliferative response to Con A (−.272) but was not reliably associated with NK cell activity (−.103).

Discussion

Two recent reviews of the literature on the relation between depression and immunity concluded with disparate positions regarding the associations between clinical depression and the immune system (Stein et al., 1991; Weisse, 1992). The results of our meta-analysis help to resolve the discrepancies. First, in support of Weisse (1992) and in contrast to Stein et al. (1991), we found that clinical depression was reliably associated with decreases in all of the measures of lymphocyte function, including proliferative responses to PHA, Con A, and PWM. In addition, a sufficient number of studies have now been published to conclude also that NK cell activity is significantly lower in clinically depressed persons. These four effects were particularly robust, and their size impressive. For example, in the methodologically restricted studies, the effects ranged from moderate (−.24) to large (−.45; see J. Cohen, 1977, for evaluation of effect sizes). Moreover, both depressed mood and severity of clinical depression were associated with the proliferative response to PHA, depressed mood was associated with NK cell activity, and severity of clinical depression was associated with proliferative response to Con A. Although the number of studies in which these latter relations were assessed is insufficient for an unequivocal conclusion, the studies do suggest a linear relation between the intensity of depressive affect and immune system functioning. The association we found between depressed mood and immunity also supports Weisse's conclusion, based on a different set of studies, that depressed affect was associated with alteration in the immune system. Weisse reviewed studies of human and nonhuman primates experiencing the disruption of a significant attachment bond, assuming that depressed mood followed the disruption.

In terms of enumerative immune outcomes, we found several associations between clinical depression and the immune system. This is in contrast to Stein et al.'s (1991) findings and goes far beyond Weisse's (1992) findings. Depression was reliably associated with a higher number of circulating white blood cells, primarily neutrophils and monocytes. The total number of lymphocytes was decreased in depression, as were the num-

[4] One approach would have been to conduct separate analyses for each scale of depressed mood that was used. The number of studies in which each scale was used in combination with specific immune parameters, however, precluded this kind of analysis.

bers of each type of lymphocyte (NK, B, and T cells) and each type of T cell (helper and suppressor/cytotoxic; however, the number of studies in which suppressor/cytotoxic T cells were assessed was too low to avoid the file drawer problem in most cases). The ratio of helper to suppressor T cells was also lower in clinically depressed subjects than in comparison subjects. It is noteworthy that only the numbers, and not the percentages, of different cell types were reliably associated with depression. In contrast to functional immune assessments, significantly stronger effects were found when studies were methodologically restricted. The majority of these effect sizes were considered to be at least moderately large (J. Cohen, 1977).

For both functional and enumerative immune parameters, effect sizes significantly increased when analyses were restricted to either older or inpatient populations (Stein et al., 1991; Weisse, 1992). Because essentially the same studies comprised both sets of analyses, it is not clear whether the large differences in immune parameters were due to aging or to hospitalization. Weisse (1992) argued that older inpatients are those with the most severe depressive symptomatology, suggesting that alterations in immune function are related to the degree of depression in both older and hospitalized depressed individuals. However, aging also has strong effects on the immune system (Sapolsky, Krey, & McEwen, 1986). Thus, alterations in immunity may be evidenced most dramatically in older depressed patient populations, because the effects of depression may be exacerbated by the effects of aging (Stein et al., 1991). Schleifer et al. (1989) found, for example, that depressed people showed decreased proliferative responses to mitogens with advancing age, whereas nondepressed controls showed increased proliferative responses. It is not clear why this would happen, although it might be due to endocrine and/or immune reactivity increasing with age. An alternative explanation lies in the effects of hospitalization. Hospitalization may influence immunity because it is stressful or because it affects other behaviors like sleep, diet, and exercise (Weisse, 1992). Unfortunately, it is not clear whether hospitalization is directly associated with immunity or exacerbates the relation between depression and immunity (as age might). Of the 14 methodologically sound studies, only 2 matched control and depressed subjects on hospitalization status.

We should point out that although we found several differences between depressed and nondepressed subjects in terms of both functional and enumerative measures of the immune system, it is difficult to interpret these outcomes with respect to health. The health consequences of changes in the enumerative immune parameters (e.g., numbers of lymphocytes in peripheral blood) have not been determined in otherwise healthy populations. Decreased NK cell activity has been related to certain human diseases (e.g., progression of cancer, chronic viral infection, and autoimmune diseases; Whiteside, Bryant, Day, & Herberman, 1990), but the health consequences of decreased proliferative responses to mitogens are less clear. In a recent study, however, it was found that compared with controls, caregivers of individuals with Alzheimer's disease had a higher incidence of depression, a decreased proliferative response to mitogens, and more days of infectious illness over 13 months (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). Two other studies have also shown that among the elderly, decreased proliferative responses to mitogens are related to increased levels of mortality and an increased number of hospitalizations (Murasko, Gold, Hessen, & Kaye, 1990; Murasko, Weiner, & Kaye, 1988). There appears to be no correlation, however, between decreased proliferative responses to mitogens and mortality or hospitalization due to specific disease entities (Murasko et al., 1990; Murasko et al., 1988). At this point, it is difficult to say whether differences in immunity between clinically depressed and nondepressed individuals have substantial implications for health (Stein et al., 1991; Weisse, 1992).

Mechanisms That Link Depression and Immunity

Why do clinically depressed subjects show immune alterations? Both neuroendocrine and behavioral mechanisms provide plausible explanations. First, clinical depression is associated with activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system (SNS; Ritchie & Nemeroff, 1991; Stokes, 1987). The activation of these pathways results in elevated serum levels of cortisol and catecholamines (Chrousos & Gold, 1992; Stokes, 1987). Immune cells have receptors for these hormones (Ader et al., 1991; Blalock, 1984, 1989; Rabin, Cohen, Ganguli, Lysle, & Cunnick, 1989), implying that they play a role in modulation of the immune system. Serum levels of cortisol, epinephrine, and norepinephrine are also directly associated with various indicators of immunity (O'Leary, 1990; Rabin et al., 1989).

Studies of neuroendocrine pathways have focused almost exclusively on a depression–cortisol–immunity pathway. Although there is strong evidence for depression–cortisol and cortisol–immunity relations (Chrousos & Gold, 1992; Dyck & Greenberg, 1991), attempts to demonstrate a depression–cortisol–immunity pathway have not been successful (Stein et al., 1991). One reason for this lack of success may be that cortisol does not mediate immune alterations in the peripheral blood of humans. Support for this view comes from two laboratory studies that found SNS-associated immune alteration in the absence of changes in serum cortisol (Landmann et al., 1984; Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991). Alternatively, it is possible that cortisol does mediate depression–immunity relations, but that two methodological issues have hindered demonstration of these links. First, the depression–cortisol–immunity pathway has been investigated only among clinically depressed persons, restricting the variance associated with the depression, cortisol, and immunity variables. Second, these studies have assessed cortisol only through the single-stick method. This reduces the power to find an effect because of the random error associated with single-stick values (Baum, Grunberg, & Singer, 1982).

An alternative pathway that could account for the relation between clinical depression and immunity involves the association of depression with specific behaviors that modulate the immune response. Depressed persons sleep less, exercise less, have poorer diets, smoke more, and use alcohol and other drugs more often than do nondepressed persons (Gregory & Smeltzer, 1983; Grunberg & Baum, 1985). These behaviors have all been shown to alter immune response (S. Cohen, Tyrrell, Russell, Jarvis, & Smith, 1992; Friedman, Klein, & Specter, 1991; Kiecolt-Glaser & Glaser, 1988; MacGregor, 1986; Simon,

1991). For example, in a recent study objective measures of sleep (e.g., sleep time, sleep efficiency, and duration of nonREM sleep) were associated with NK cell activity independent of depression (Irwin, Smith, & Gillin, 1992).

The association of depression with immunity might therefore be accounted for by the fact that the health practices of clinically depressed subjects are different from those of controls (Weisse, 1992). Although many clinical depression–immunity studies have focused on physically healthy, drug-free (i.e., antidepressant-free) subjects, relations between health behaviors and depression or immunity have generally not been assessed. Exceptions are studies conducted by Schleifer et al. (1989) and Irwin and colleagues (Irwin et al., 1990; Irwin, Smith, & Gillin, 1987). For example, Schleifer et al. statistically controlled for weight and recent weight loss and found these did not alter the depression–immunity associations. Irwin and colleagues found no relation between alcohol intake and depression or immunity (i.e., NK cell activity and number of white blood cells, neutrophils, monocytes, and lymphocytes). However, they did find that depressed individuals smoked more than controls and, furthermore, that cigarette use was the strongest predictor of the number of neutrophils and lymphocytes in circulation. Controlling for cigarette use and alcohol intake, however, did not affect the association between depression and NK cell activity. In sum, health practices provide a plausible pathway through which depression might influence some immune parameters. In the future, researchers will have to bear these important variables in mind and be aware that depressive affect may not have a large effect independent of life-style variables.

Designing Studies of Depression–Immunity Associations

The present meta-analysis not only resolves the discrepancies between Weisse's (1992) and Stein et al.'s (1991) reviews of the depression–immunity literature, but also provides needed information on the design of studies in this area. First, an approximation of the sample size needed to conduct a clinical depression–immunity study can be derived from the analyses. We used effect sizes derived from the set of methodologically restricted studies, for example, to calculate the sample sizes needed to detect the correlation by two-tailed tests at $p < .05$ and a power of .80 (J. Cohen, 1977). Using these effect sizes, a total sample size of approximately 138 (including both patients and controls) would be required to detect differences in proliferative response to PHA ($r = .24$) and NK cell activity ($r = .25$); 84 subjects would be needed to detect differences in the number of circulating B cells ($r = .29$); 65 subjects would be needed to detect differences in proliferative response to Con A ($r = .36$); and between 30–40 subjects would be required to detect differences in the proliferative response to PWM, the helper:suppressor ratio, and the numbers of circulating neutrophils, T cells, and helper T cells ($rs = .45$–$.80$).

Second, there is now suggestive evidence that alterations in immunity are related to the severity of depressive symptoms in both clinical and nonclinical populations. Therefore, researchers need to assess the degree of negative affect to determine whether it is related to the degree of immune alteration. To do this, researchers should use a nonclinical rating scale of negative affect on both the depressed and control groups. We also need to understand more about other characteristics of depression that might be related to immune alteration. For example, the diagnosis of major depression represents a group of heterogeneous affective syndromes with several subtypes that have different biological correlates (Stein et al., 1991; Weisse, 1992). Different subtypes might be differentially associated with alterations in immunity. This is an issue we were unable to examine in the present meta-analyses because only one methodologically sound study included more than one diagnostic subtype.

Third, the effects of aging and hospitalization need to be teased apart in a methodologically sound design. To do this, researchers need to match depressed inpatients and outpatients with controls on both age (using a relatively wide age range) and hospitalization status. In the present meta-analyses, we found significantly stronger effects among older patients and hospitalized patients, but we could not determine the separate effects of age and hospitalization. We also need to determine the stability of depression–immunity associations across other demographic factors, such as gender and race. Although we found reliable effects across studies that included both men and women, neuroendocrine and immune gender differences do exist. For example, Evans et al. (1992) found immune differences between depressed and control groups only for men (although insufficient power may have accounted for the absence of group differences in women).

Careful consideration should be given to the immune outcomes included in a study. Because we understand better what the results of functional tests represent than what the results of enumerative tests represent, the former are preferable to the latter. Functional tests are available that assess cell types whose function has not been a focus of investigation in the depression literature. For example, there are functional tests for neutrophils and monocytes (or macrophages; Stites, 1991). Many of these functional assays, however, are performed in vitro (outside the body), in environments that are quite different from the body's in terms of endocrine and other physiological influences. Thus, we do not know how well these functional assays reflect in vivo (in the body) cellular functions. Some functional tests are available, however, that do directly reflect in vivo immune function. One of these is the assessment of the production of antigen-specific Ab (Stites, 1991), which involves administering a nonpathogenic antigen to subjects and then quantifying the amount of specific Ab that is produced to that antigen (Glaser, Kiecolt-Glaser, Bonneau, Malarkey, & Hughes, 1992; Stone, Cox, Valdimarsdottir, Jandorf, & Neale, 1987). Another is delayed-type hypersensitivity, which involves determining a nonpathogenic antigen (e.g., tetanus) to which subjects have previously been exposed, administering a small amount of the antigen just below the skin (usually the arm), and then quantifying the subsequent inflammation produced by the immune response (Stites, 1991). The stronger the inflammatory response, the more fully the cellular arm of the immune system is assumed to be functioning. Because deficits in this function occur only with fairly severe changes in immunity, however, the subtle influences of affective states are not seen using this test.

Finally, several general methodological points are important regarding the design of studies of depression–immunity rela-

tions. Immune assessments of depressed and control subjects should be done simultaneously, and the day of testing should be statistically controlled (Schleifer et al., 1989; Stein et al., 1991). Statistical analysis should also take into account the use of multiple effector-to-target ratios (in the NK cell activity assay) or multiple mitogen concentrations (in the lymphocyte proliferation assay). Depressed patients should be given a comprehensive health screen to rule out an organic cause for their affective illness; control subjects should be given a psychiatric screen to ensure their psychological health. Control subjects should also be free of a history of psychiatric illness to rule out the possibility that their current physiological environment is affected by that history (Henriques & Davidson, 1990). All subjects should be drug free (i.e., prescription, over-the-counter, and illicit drugs) at the time of assessment to ensure that immune alterations are not a result of drugs (Stein et al., 1991; Weisse, 1992). Finally, immune system functions and enumerations and endocrine assessments are easily influenced by a variety of factors (Baum et al., 1982; Stites, 1991). Therefore, we recommend incorporating multiple assessments of subjects to increase the reliability of the characterization of an individual's physiologic environment, and hence, increase our understanding of the associations among affective, neuroendocrine, behavioral, and immune parameters.

Conclusion

By using meta-analysis to review studies of the associations between depression and immunity, we resolved a conflict between two recent reviews of the literature (Stein et al., 1991; Weisse, 1992) and showed strong and reliable effects for the enumerative and functional immune parameters assessed in the studies. What implications do these findings have for the association between depression and physical health? Little is known about normal variation in immunity and how it relates to disease. Thus, it is not possible to examine a person's immune system and predict disease resistance or susceptibility (Calabrese et al., 1987; S. Cohen & Williamson, 1991; Stein et al., 1991; Weisse, 1992). One might argue, however, that the decreased immune function associated with depression would be related to increased susceptibility to immune-mediated diseases (e.g., cancer and infectious or autoimmune diseases). Empirical support for this is sparse, although some evidence prospectively linking depression to cancer morbidity and mortality exists (Linkins & Comstock, 1990; Persky et al., 1987; Shekelle et al., 1981). Studies are needed that link variations in affective state to indicators of immunity and then to disease outcomes.

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Appendix

Studies Included in the Clinical Depression Meta-Analyses

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* Study met criteria for methodological soundness.

Studies Included in the Depressed-Mood Meta-Analyses

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