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REVIEW ARTICLE

The Relationship of Depression and Stressors to Immunological Assays: A Meta-Analytic Review

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This is a broad meta-analysis of the relations of both depression and stressors to immunological assays. The number of study samples (greater than 180) and measures (greater than 40) is much more extensive than any so far. Analyses are done by both fixed and random effects. By a fixed-effects analysis, both major depression and naturally occurring acute stressors are associated with (1) an overall leukocytosis, (2) mild reductions in absolute NK-cell counts and relative T-cell proportions, (3) marginal increases in CD4/CD8 ratios, and (4) moderate decreases in T- and NK-cell function. However, the degree of heterogeneity of the studies' results raises questions about their robustness. Therefore, we also did the first random effects analysis to estimate what is likely to appear in future studies. For depression, the analysis showed the immunological correlates included (1) an overall leukocytosis, manifesting as a relative neutrophilia and lymphoenia; (2) increased CD4/CD8 ratios; (3) increased circulating haptoglobin, PGE_2, and IL-6 levels; (4) reduced NK-cell cytotoxicity; and (5) reduced lymphocyte proliferative response to mitogen. For stressors, the random effects analysis showed that future studies are likely to find the following effects: (1) an overall leukocytosis, manifesting as an absolute lymphocytosis; (2) alterations in cytotoxic lymphocyte levels, CD4/CD8 ratios, and natural killer cell cytotoxicity with the direction of change depending on the chronicity of the stressor; (3) a relative reduction of T-cell levels; (3) increased EBV antibody titers; (4) reduced lymphocyte proliferative response and proportion of IL-2r bearing cells following mitogenic stimulation; and (5) increased leukocyte adhesiveness. The random-effects analysis revealed that for both major depression and naturally occurring stressors the following effects are shared: leukocytosis, increased CD4/CD8 ratios, reduced proliferative response to mitogen, and reduced NK cell cytotoxicity. The implications for these findings for disease susceptibility and the pathophysiology of these conditions is discussed.

Key Words: immunological assays; depression; stressors; meta-analysis of measures.

INTRODUCTION

An increasing body of evidence shows that certain psychological states and experiences are associated with variations in immune parameters (Ader, Felten, & Cohen, 1991; Locke, 1982; Weisse, 1992). The two states that have been studied most intensively are major depression and stressors. In separate meta-analytic reviews of studies conducted through 1991, Herbert and Cohen (1993a, 1993b) found that these were significantly associated with virtually all of the immune measures included in the reviews. In most cases where significant findings were obtained, both depression and stressors were associated with decreases in the immune parameters. Many additional studies on the relationship of depression or stressors to immunological assays have been published since 1991; some of these feature a wider range of immune measures

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and improved technology than was typically found in earlier studies. Therefore, it seems an appropriate time to reevaluate the findings.

In addition to including more studies and a wider range of immune measures, our review has other advantages over previous effort. First, we have actually conducted two reviews, one on depression and the other on stressors, which makes it possible to discuss similarities and differences in findings for each factor. Second, findings for depression and for stress have been summarized in two ways: (a) a fixed effect meta-analysis, similar to that conducted by Herbert and Cohen (1993a, 1993b), that allows generalization to other subjects like those drawn from the samples in reviewed studies (Rosenthal, 1995); and (b) a random effect meta-analysis that allows generalization to future studies (Rosenthal, 1995). The random effect approach, which has not been used in prior reviews, may be the most informative analysis because it indicates the range of effect sizes that are likely to be observed in future studies. Third, this article is the first to examine the moderator variables, the robustness of observed effects, and the degree of heterogeneity in the findings.

METHOD

Criteria for Selecting Samples

Samples that were included met these inclusion/exclusion criteria: used only physically healthy subjects; were published in peer-reviewed journals; diagnosed as major depression by RDC (Spitzer, Endicott, & Robins, 1978), *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.) (American Psychiatric Association, 1980), or *DSM-III-R* (1987); and excluded medicated and bipolar patients. Finally, studies of stressors had to have ''objective'' stressor measures (e.g., a standard life event scale for naturalistic stressors or an experimental stressor) as opposed to indicators of the subjective response to stressors. Studies of stressors that included physical components (e.g., weightlessness) were excluded. If samples overlapped across studies, the smaller study group was excluded. If more than one sample was included in a study, the samples were treated separately. Immune measures were included that were examined by at least two studies.

Measures

The immune measures. Those reviewed here are highly diverse; they were grouped into the following categories: major leukocyte classes, cell surface markers, humoral factors, and functional measures. The limited length of our review prevents inclusion of a description of the functional significance of the various immune measures or a discussion of potential psychobiological mechanisms that might link major depression or exposure to stressors to immunological assays. Excellent discussions of these issues can be found in Herbert and Cohen (1993a, 1993b); O'Leary (1990); Maier, Watkins, and Fleshner (1994); Maes (1995); and Maes, Smith, and Sharpe (1995).

The depression measures. We only included individuals with a diagnosis of depression. Measures of severity of depression were diverse; but most commonly used was the observer-rated Hamilton Depression Rating Scale (HDRS; Hamilton, 1960).

The stressor measures. A major division of the stressor studies was (a) studies of stressors as they occur naturally (i.e., observational studies) and (b) studies of stressors as they are artificially administered (i.e., experimental studies). For naturalistic studies, the most common measures ($n = 16$ studies) were self-reported life events

(Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978; Holmes & Rahe, 1967) and hassles (DeLongis, Coyne, Dakof, Folkman, & Lazarus, 1982). A large minority of observational studies used single, discrete stressors (e.g., examinations) rather than self-report of stressful events.

Meta-Analytic Techniques

Average effect sizes. All mathematical and statistical operations were performed on Fisher's *Z*'s because of their superior distributional properties. For each relation, indices of central tendency were calculated: unweighted and weighted mean *r*'s, the median *r,* and the percentage of studies which found effects in the same direction as the mean weighted *r.* Weighted average effect sizes were computed as *r*'s by proportionally weighting each study's observed effect size according to its degrees of freedom (*df*). Explicitly, this procedure gives more weight to larger studies, which tend to obtain more reliable estimates of the population effect size (Rosenthal, 1991). Effect sizes for each study were calculated from inferential statistics when possible. If inferential statistics were not presented, descriptive statistics were used to calculate the study's Hedge's *g,* which was then converted to an *r.* To be conservative, one-tailed significance levels of $p = .05$ were assigned to studies with no quantifiable results that reported significant results. Advantages of reporting meta-analytic results as *r*'s as opposed to other effect size indicators (e.g., Cohen's *d* and Hedge's *g*), have been discussed by Rosenthal (1991).

Robustness of effects. To facilitate comparison of robustness of effects, we calculated coefficients of robustness (CR) for each relation (Rosenthal, 1991). CR's with large absolute magnitudes tend to be associated with relations for which studies consistently observe similar effect sizes and/or for which studies observe larger effect sizes, with the sign of the CR indicating the direction of the effect. Because the CR is independent of the cumulative number of studies or subjects, it allows descriptive comparisons that are not confounded by which relations have received more attention in published research; in this sense the CR is unlike results of significance tests and a useful complement to them.

Significance tests. To determine whether average effect sizes were statistically significant, we performed both fixed effect and random effect analyses. A fixed effect approach uses the cumulative number of subjects (*N*) as the basis for the *df* for the statistical test; thereby, it effectively treats the observations as if they come from one large, homogeneous study. Though the fixed effect analysis offers considerable power, generalizations from it are limited to those individuals who may have participated in the very same studies in the review (and who are like those individuals who participated) (Rosenthal, 1995). Fixed effect analyses do not account for between-study variability when determining statistical significance. We used a modification of the Stouffer method (*df* weighting of standard normal deviates) to obtain fixed effect *p* values (Rosenthal, 1991).

A random effect approach uses the cumulative number of independent samples (*k*) as the basis for the *df* for the statistical test. Though the random effect approach generally has less power than the fixed effect approach, it offers increased generalizability. Using a random-effect approach to the results, we calculated a 95% confidence interval based on the samplewise standard deviation using samples, rather than subjects, as the sampling unit. This interval gives the range of effect sizes that future studies, like those reviewed here, are very likely to find. A random effect approach

explicitly accounts for between-sample variability in determining whether future studies are likely to find an effect.

Tests of heterogeneity. To determine whether observed effect sizes were more heterogeneous than expected by chance variation, we performed chi-squared tests for each relation. The significance of each test was assessed in relation to the number of studies which examined that relation. Significant findings indicate that observed effect sizes differ by more than chance variation. Sources of heterogeneity include differences in important moderator variables or sample size between studies; more worrisome for meta-analysis, significant heterogeneity may indicate that the studies are drawn from dissimilar ''samples'' of studies (e.g., the specified dependent and/or independent variables differ substantially). Because of this possibility, some advise caution in interpreting meta-analytic results when findings are heterogeneous (Hedges & Olkin, 1985). Others (Rosenthal, 1991), however, argue that significant heterogeneity *compels* the investigator to search for moderators.

Moderator variable analysis. To examine the possibility that subject or procedural characteristics moderated the relations of depression and/or stressors to immunity and thereby contributed to studywise heterogeneity, we performed nonparametric random effect contrasts (i.e., Spearman rank correlations and Kruskal–Wallis tests). It should be emphasized that the moderator analyses that were performed were random-, rather than fixed-, effect analyses. A caveat which should be considered in interpreting the random effect analyses is that samples were unlikely to have been selected on the basis of the moderator characteristics. Therefore, some observed effects might be skewed if the dependent variable was related to convenience factors in subject recruitment. Additionally, with the present data set, many more moderator effects would likely be significant under a fixed effect analysis due to its greater power. Given the many immune variables included in this article, however, a full test of all possible fixed effect interactions associated with the identified moderator variables is beyond its scope. A fixed-effect examination of moderators really deserves a separate publication.

To reduce the number of tests performed, we limited our random effect analyses to those relations represented by eight or more samples (120 and 80 correlations for depression and stressor studies, respectively). Significance tests for all contrasts are two-tailed. For significant relations, studies were blocked according to their rank to assist interpretation of the interaction. Significant results from these exploratory analyses should be interpreted cautiously because of the numerous tests performed; they warrant independent replication.

In the depression studies, the potential sample moderator variables examined were gender (percentage of female subjects), age (mean sample age), ambulatory status (defined as $>75\%$ inpatient, 25–75% inpatient, or $<25\%$ inpatient); and depression severity (mean HRSD score) as well as the degree to which controls were matched to the study group on gender and age. In the stressor studies, the potential moderator variables that were examined were also usual ones: gender, age, temporal duration of the stressor (i.e., hyperacute: <3 h vs acute or chronic: >3 h), nature of the stressor (i.e., experimental vs naturally occurring), and source of information about the stressor (i.e., self-report vs objectively verified).

RESULTS

In summarizing studies of the relations of depression and stressors to immunological assays, we present the following information: (a) results of fixed-effect meta-

analysis, (b) results of random-effect meta-analysis, (c) results of heterogeneity analyses, and (d) results of random-effect moderator analyses.

Depression and Immunological Assays

Fixed-effect meta-analysis. Under a fixed-effect model, significant results were obtained for each major immune cell class measure (see Table 1). Collectively, these findings indicated a neutrophilic leukocytosis in depression, with a concomitant relative lymphopenia and monocytopenia (i.e., a proportional reduction of lymphocytes and monocytes). Effect sizes (*r*'s) ranged from −.09 to −.49 for measures negatively associated with depression (percentages and numbers of monocytes and lymphocytes) and from .16 to .55 for measures positively associated with depression (leukocytes and percentage and number of neutrophils). Despite the presence of a relative monocytopenia, there was evidence of a very slight, but reliable, *absolute* monocytosis ($r = .04$), which evidently was overshadowed by the much larger neutrophilia.

Significant results were obtained with 9 of the 15 cell surface markers. Absolute NK and relative T-cell levels were negatively associated with depression (*r*'s = −.07 and −.12), whereas relative B-cell levels, CD4 levels, CD4/CD8 ratios, and levels of cells bearing activation markers (i.e., % HLA-DR$^+$, % and no. CD25$^+$, and no. HLA-DR$^+$) were positively associated with depression (*r*'s = .12 to .43).

Significant results were obtained for 9 of the 11 humoral factors. A general decrease in total serum protein levels was observed ($r = -.62$), accompanied by a decrease in the negative acute phase plasma protein albumin ($r = -.55$). In contrast, serum levels of the following positive acute phase plasma proteins were elevated: haptoglobin, α1-acid glycoprotein, and α1-antitrypsin (*r*'s = .26 to .45). Finally, circulating levels of IgM, PGE2, IL-6, and sIL-2r also were elevated (*r*'s = .28 to .60).

Significant results also were obtained with five of the six functional measures (lymphocyte proliferative response to Con A, PWM, and PHA; neutrophil phagocytosis; and NK cytotoxicity); in each case, depression was associated with decreased cellular immune function (*r*'s = −.20 to −.36).

Random-effect meta-analysis. Under a random-effect model, fewer relations were significant, as indicated by confidence intervals that excluded zero. Still, significant findings demonstrated a lymphopenia, accompanied by a relative neutrophilia, an increased CD4/CD8 ratio, increased circulating haptoglobin levels, and decreases in four indices of cellular immune function (i.e., NK cytotoxicity and lymphocyte proliferative response to PHA, Con A, and PWM). No other relations were significant under the random-effect model.

Heterogeneity analyses. Considerable heterogeneity was observed in findings for virtually all major immune cell class and functional measures. This was the case even for most relations that were significant under the more generalizable random-effect analysis. Heterogeneity was less pronounced for findings pertaining to cell surface markers and humoral factors.

Random-effect moderator analysis. Significant results from these analyses are summarized in Table 2. Studies of depression with a higher percentage of females showed (a) greater increases in B- and T-cell numbers, (b) smaller decreases in NK cell cytotoxicity, and (c) greater deficits in Con A responsiveness. Age did not demonstrate a significant moderating effect with any of the immune variables. Ambulatory status acted as a moderator variable in several cases. Specifically, depression was positively related to proportions of CD4 cells in inpatients, but was negatively associ-

TABLE 1
Diagnostic Depression in Relation to Immune Measures

Immune measure	Size of analysis: Samples (*k*)	Size of analysis: Subjects (*N*)	Size of analysis: Median sample size	Indices of central tendency: Weighted mean *r*	Indices of central tendency: Unweighted mean *r*	Indices of central tendency: Median *r*	Indices of central tendency: % in direction of mean *r*	Standard deviation: Weighted *SD*	Standard deviation: Unweighted *SD*	Coefficient of robustness: Weighted CR	Coefficient of robustness: Unweighted CR	Fixed effect Overall *p*	Random effect: Overall *p*	Random effect: 95% CI From	Random effect: 95% CI To	Heterogeneity: X^2	Heterogeneity: *p* of X^2
Major immune cell classes																	
Leukocytes	24	1510	45	0.187	0.265	0.267	79	0.370	0.360	0.53	0.77	**1.0E-6**	**0.001**	0.118	0.399	155.1	1.4E-21
No. lymphocytes	22	1527	47	−0.184	0.009	0.000	55	0.352	0.299	−0.52	0.03	**<1.0E-35**	0.89	−0.124	0.141	202.7	1.1E-31
No. monocytes	14	1126	53	0.037	0.179	0.001	57	0.403	0.380	0.09	0.47	**0.01**	0.11	−0.050	0.390	141.0	1.4E-23
No. neutrophils	11	1002	60	0.271	0.233	0.317	82	0.354	0.352	0.77	0.66	**<1.0E-35**	0.06	−0.010	0.449	83.4	1.1E-13
% lymphocytes	11	826	40	−0.479	−0.215	−0.155	73	0.393	0.260	−1.22	−0.83	**<1.0E-35**	**0.03**	−0.378	−0.039	75.9	3.1E-12
% monocytes	9	744	40	−0.154	−0.103	−0.151	55	0.275	0.270	−0.56	−0.38	**1.4E-5**	0.33	−0.323	0.128	16.5	0.04
% neutrophils	8	777	48	0.537	0.315	0.232	10	0.365	0.243	1.47	1.30	**<1.0E-35**	**0.01**	0.119	0.487	69.4	1.9E-12
Cell surface markers																	
No. B	12	661	33	0.016	0.028	0.070	67	0.281	0.280	0.06	0.10	0.06	0.74	−0.154	0.208	33.7	0.0004
No. CD3	16	879	40	0.011	0.014	0.000	44	0.212	0.212	0.05	0.07	0.19	0.80	−0.099	0.126	30.2	0.01
No. CD4	16	928	43	0.032	0.018	0.005	50	0.140	0.140	0.23	0.13	0.15	0.62	−0.057	0.092	17.7	0.28
No. CD8	15	885	42	−0.045	−0.046	−0.104	53	0.187	0.187	−0.24	−0.24	0.55	0.36	−0.150	0.059	24.3	0.04
No. NK	10	432	33	−0.069	0.003	0.025	50	0.206	0.303	−0.34	0.01	**0.01**	0.97	−0.211	0.216	38.4	1.4E-5
No. CD25	2	63	32	0.410	0.422	0.419	100	0.133	0.131	3.08	3.22	**0.0008**	0.13	−0.625	0.927	0.5	0.49
No. HLA-DR	2	99	50	0.430	0.449	0.448	100	0.095	0.085	4.54	5.28	**2.6E-5**	0.08	−0.275	0.848	0.3	0.61
% B	10	527	37	0.118	0.062	0.153	60	0.356	0.351	0.32	0.18	**3.7E-5**	0.60	−0.197	0.315	43.3	1.9E-6
% CD3	12	549	35	−0.121	−0.140	−0.030	50	0.311	0.310	−0.39	−0.45	**0.05**	0.20	−0.331	0.062	36.3	0.0002
% CD4	15	617	38	0.130	0.103	0.000	40	0.302	0.301	0.43	0.34	**9.6E-5**	0.22	−0.068	0.269	42.7	9.6E-5
% CD8	14	559	36	−0.120	−0.174	0.000	43	0.351	0.347	−0.34	−0.50	0.12	0.10	−0.367	0.033	58.9	8.2E-8
% NK	6	225	33	−0.021	0.005	0.000	33	0.255	0.253	−0.08	0.02	0.24	0.26	−0.384	0.138	15.3	0.01
% CD25	2	63	32	0.237	0.254	0.251	100	0.168	0.167	1.41	1.52	**0.04**	0.27	−0.850	0.944	0.8	0.38
% HLA-DR	4	146	26	0.155	−0.063	0.059	50	0.578	0.544	0.27	−0.12	**0.002**	0.85	−0.775	0.720	31.1	8.3E-7
CD4/CD8 radio	16	834	39	0.186	0.167	0.151	63	0.258	0.257	0.72	0.65	**0.001**	**0.02**	0.029	0.300	28.1	0.02
Humoral factors																	
Total serum protein	4	129	29	−0.617	−0.645	−0.543	100	0.455	0.452	−1.36	−1.46	**<1.0E-35**	0.06	−0.913	0.010	19.3	0.0002
α_1-Acid glycoprotein	6	289	38	0.301	0.233	0.263	83	0.299	0.286	1.01	0.81	**8.0E-8**	0.11	−0.071	0.497	17.1	0.004
α_1-Antitrypsin	5	164	34	0.261	0.328	0.207	100	0.361	0.353	0.72	0.93	**0.002**	0.11	−0.117	0.614	10.8	0.03
Haptoglobin	7	290	41	0.450	0.497	0.462	100	0.188	0.177	2.40	2.81	**1.2E-13**	**0.0002**	0.362	0.611	7.7	0.26

Albumin	4	164	37	−20.545	−20.591	−20.433	100	0.488	0.483	−21.12	−21.22	**<,1.0E-35**	0.09	−20.908	0.158	22.8	4.4E-5
IgM	7	483	41	0.275	0.190	0.143	71	0.249	0.231	1.10	0.82	**<,1.6E-10**	0.07	−20.025	0.388	51.6	2.3E-9
IgG	4	377	48	−20.070	−20.079	−20.072	75	0.071	0.070	−21.00	−21.12	0.91	0.11	−20.188	0.032	0.5	0.92
IgA	6	442	40	−20.002	0.068	0.038	50	0.140	0.117	−20.02	0.58	0.73	0.21	−20.055	0.189	3.7	0.59
PGE_2	4	117	26	0.522	0.544	0.570	100	0.170	0.167	3.06	3.26	**3.7E-8**	**0.01**	0.328	0.705	1.8	0.63
IL-6	4	217	47	0.370	0.354	0.222	100	0.200	0.180	1.77	1.58	**3.3E-8**	**0.05**	0.001	0.523	6.1	0.11
sIL-2r	5	275	46	0.602	0.624	0.445	100	0.632	0.632	0.95	0.99	**2.4E-15**	0.10	−20.191	0.930	96.3	9.8E-21
Functional measures																	
Neutrophil phagocytosis	3	112	36	−20.321	−20.399	−20.176	100	0.475	0.466	−20.63	−20.86	**0.004**	0.28	−20.932	0.681	13.5	0.001
NK cytotoxicity	16	896	39	−20.345	−20.340	−20.372	81	0.259	0.267	−21.33	−21.27	**3.3E-9**	**0.0002**	−20.462	−20.221	138.5	4.5E-22
PHA	25	1144	40	−20.263	−20.326	−20.279	81	0.401	0.396	−20.66	−20.82	**7.0E-10**	**0.0005**	−20.417	−20.147	142.7	7.4E-19
Con A	19	941	42	−20.205	−20.339	−20.341	79	0.421	0.400	−20.49	−20.85	**9.4E-10**	**0.0002**	−20.527	−20.148	76.8	3.1E-9
PWM	14	756	41	−20.222	−20.305	−20.301	86	0.278	0.263	−20.80	−21.16	**4.2E-6**	**0.0008**	−20.438	−20.153	45.6	1.7E-5
IL-2 production following stimulation	4	102	28	−20.113	−20.206	−20.258	75	0.326	0.309	−20.35	−20.67	0.23	0.28	−20.615	0.291	18.9	0.06

Note. Effect sizes which differ reliably from zero ($p < .05$) are shown in bold with their respective probability levels.

Glossary for Tables 1 and 3. 95% confidence interval (CI): Calculated using a random-effect approach, this interval gives the range of effect sizes that future studies are very likely (95% of the time) to find.

Coefficient of robustness (CR): A statistic which indicates the robustness of observed effect that, unlike *p* values, is not confounded by the cumulative number of studies or subjects. CR's are calculated as the ratio of a measure's mean effect size divided by its standard deviation.

Heterogeneity: The degree to which observed effect sizes differ from one another more than expected by chance alone. Sources of heterogeneity include differences in important moderator variables or sample size between studies. More troubling for meta-analysis, significant heterogeneity may indicate that the studies are drawn from dissimilar ''samples'' of studies (e.g., the specified dependent and/or independent variables differ substantially).

Fixed-effect analyses: A fixed-effect approach uses the cumulative number of subjects (*N*) as the basis for the *df* for the statistical test. Thus, it effectively treats the observations as if they come from one large, homogeneous study. Though the fixed-effect analysis offers considerable power, generalizations from it are limited to those individuals who may have participated in the very same studies in the review (and who are like those individuals who participated). Fixed-effect analyses do not account for between-study variability when determining statistical significance.

Random-effect analyses: A random-effect approach uses the cumulative number of independent samples (*k*) as the basis for the *df* for the statistical test. Though the random-effect approach generally has less power than the fixed-effect approach, it offers increased generalizability. A random-effect approach explicitly accounts for between-sample variability in determining whether future studies are likely to find an effect.

Weighted/unweighted: Refers to whether calculation of the statistic was weighted with respect to each study's sample size. ''Weighting'' gives more weight to larger studies.

TABLE 2
Random Effects of Moderator Analyses in Studies of Depression

Moderator variable	Immune measure	Number of study groups	Spearman *r*	Two-tailed $p <$
Subject characteristics				
Sex (% female)	Total B	12	.74	.01
	Total CD3	16	.64	.01
	NK activity	16	.64	.01
Age	None			
Ambulatory status	PWM	14	−.69	.01
(1 = inpatient; 0 = outpatient)	%CD4	15	.51	.05
	%B	10	−.62	.05
Severity of depression	Total CD8	15	.66	.01
	%CD3	12	.57	.05
	%CD4	15	.51	.05
Matching characteristics				
Underrepresentation of females in control samples	CD4/CD8	16	.64	.01
Younger controls than depressed patients	CD4/CD8	16	.65	.01

ated with CD4 proportions among outpatients. Studies with depressed outpatients found increased proportions of B cells, whereas studies of inpatients tended to find that depression was associated either with decreased B-cell proportions or no change in B cells. Depression also was associated with bigger functional deficits in PWM response in studies of inpatients than in studies of outpatients. Studies with severely depressed samples showed smaller reductions in CD8 cell counts, smaller reductions in proportions of T cells, and greater increases in proportions of $CD4^+$ cells relative to studies with less depressed samples. Finally, studies in which controls were poorly matched to depressed patients on gender (higher percentages of females in depressed group) and age (greater in depressives than in controls) were more likely than studies with better matched controls to find increased CD4/CD8 ratios in the depressed group.

Stressors and Immunological Assays

Fixed-effects meta-analysis. Under a fixed-effect model (see Table 3), significant results were obtained with two of the seven major immune cell measures. Specifically, stress-associated increases in lymphocyte counts appear to be associated with a total leukocytosis ($r = .14$) in the context of a relative neutropenia ($r = -.26$).

Significant results were obtained with 7 of the 13 cell surface markers. Relative CD3, CD8, and NK cell levels; total CD4 counts; and CD4/CD8 ratios were negatively associated with stressors (r's = −.08 to −.19). In contrast, absolute CD8 and NK cell counts were positively associated with stressors (r's = .19 and .52).

Significant results were obtained with two of the five humoral factors; EBV and HSV antibody titers were positively associated with stressors (r's = .36 and .38). Significant results also were obtained for six of the seven functional measures; stres-

sors were associated with decreases in proliferative response to PHA and Con A, NK cytotoxicity, and IFN production and IL-2r receptor (IL-2r) induction following mitogenic stimulation (r's = −.19 to −.66). Finally, stress-related increases in leukocyte adhesiveness were observed as well (r = .45).

Random-effect meta-analysis. Under a random-effect model, there once again was a decrease in the number of significant findings, though no effect sizes were reliably smaller than under fixed-effect analyses. A leukocytosis, resulting from an absolute lymphocytosis was observed. Significant findings were also obtained for four of the cell surface markers (absolute CD8 and NK counts, relative CD3 levels, and CD4/CD8 ratio), one humoral factor (EBV antibody titers), and five measures of cellular immune function (proliferative response to PHA, Con A, and PWM; IL-2r induction following mitogenic stimulation; and leukocyte adhesiveness).

Heterogeneity analyses. Considerable heterogeneity was observed in findings for virtually every major immune cell measure and humoral factor. This variability extends to those measures that were significant in the random-effects analysis. Heterogeneous findings were somewhat less pronounced for the cell surface markers and functional measures.

Random-effect moderator analysis. Significant results from these analyses are summarized in Table 4. Additionally, complete subanalyses according to stressor chronicity are shown in Table 3 for those variables that exhibited a trend ($p < .10$) for this moderator variable. Studies with a higher percentage of female subjects than with fewer females found stronger positive relations between stressors and numbers of lymphocytes, CD3 cells, and CD4 cells. Studies with older subjects than with younger subjects found stronger positive relations between stressors and number of CD4 cells. Studies with hyperacute stressors found positive relations between stressors and numbers and percentages of NK cells and percentages of CD8 cells, whereas acute/chronic stressors were inversely related to these lymphocyte subsets. Similar trends were obtained for NK cytotoxicity where hyperacute stressors were associated with increased lytic activity and acute/chronic stressors were associated with decreased lytic activity. Corresponding to these results, hyperacute stressors were associated with reduced CD4/CD8 ratios, whereas acute and chronic stressors were associated with increased CD4/CD8 ratios. The experimental vs naturalistic stressor distinction yielded identical differences as were obtained with the hyperacute vs acute/chronic distinction; this likely reflects that almost all hyperacute stressors were experimenter-induced. Collinearity prevented us from performing mediational analyses to explore these relations. No moderator effects were observed with self-reported vs objectively-verified stressors.

DISCUSSION

This article is the most comprehensive quantitative review of the relationship of depression and stressors to immunological assays. The number of study groups (>180) and measures (>40) examined considerably exceeds those presented in prior reviews (Herbert & Cohen, 1993a, 1993b; Stein, Miller, & Trestman, 1991, Weisse, 1992). Also, we followed Rosenthal's (1995) recommendation that meta-analyses include both fixed- and random-effect types of inferential testing because each answers a different question and makes different contributions. The fixed effect approach generally provides greater statistical power, but the results generalize only to similar subjects who might have been included in the studies in the analysis. In con-

TABLE 3
Stressors in Relation to Immune Measures

	Size of analysis			Indices of central tendency				Standard deviation		Coefficient of robustness			Random effect			Heterogeneity	
														95% CI			
Immune measure	Samples (*k*)	Subjects (*N*)	Median sample size	Weighted mean *r*	Unweighted mean *r*	Median *r*	% in direction of mean *r*	Weighted *SD*	Unweighted *SD*	Weighted CR	Unweighted CR	Fixed effect Overall *p*	Overall *p*	From	To	X^2	*p* of X^2
Major immune cell classes																	
Leukocytes	21	1285	44	**0.141**	**0.169**	0.090	.62	0.252	0.257	0.56	0.66	**0.0002**	**0.008**	0.051	0.283	51.3	0.0001
No. lymphocytes	18	626	27	0.093	**0.194**	0.046	.50	0.329	0.323	0.28	0.60	0.20	**0.02**	0.029	0.347	63.4	2.9E-7
No. monocytes	6	341	51	0.059	0.075	0.065	.67	0.076	0.082	0.77	0.92	0.18	0.08	−0.011	0.160	2.0	0.85
No. neutrophils	3	62	18	0.074	0.008	0.205	.67	0.470	0.465	0.16	0.02	0.19	0.98	−0.846	0.851	8.8	0.01
% lymphocytes	4	80	15	−0.002	−0.010	0.000	.25	0.377	0.377	−0.01	−0.03	0.74	0.96	−0.566	0.552	18.6	0.0003
% monocytes	4	58	15	−0.157	−0.111	−0.119	.75	0.324	0.320	−0.48	−0.35	0.11	0.55	−0.564	0.394	3.7	0.30
% neutrophils	5	98	18	**−0.256**	−0.076	0.000	.40	0.444	0.405	−0.58	−0.19	**0.005**	0.71	−0.544	0.428	14.9	0.005
Cell surface markers																	
No. B	12	329	19	−0.199	−0.069	−0.030	.50	0.348	0.339	−0.57	−0.20	0.99	0.07	−0.014	0.394	22.5	0.02
No. CD3	18	609	22	**−0.070**	0.073	0.000	.39	0.386	0.373	−0.18	0.20	**0.008**	0.44	−0.120	0.263	31.9	0.02
No. CD4	26	946	32	**−0.134**	−0.079	0.000	.38	0.268	0.267	−0.50	−0.30	**2.0E-5**	0.16	−0.187	0.032	43.7	0.01
No. CD8	24	873	28	**0.188**	**0.283**	0.275	.75	0.273	0.261	0.69	1.08	**6.4E-6**	**3.0E-5**	0.175	0.382	38.7	0.02
Hyperacute stressors	16	534	20	**0.270**	**0.333**	0.388	.87	0.236	0.233	1.15	1.43	**<1.9E-7**	**4.0E-5**	0.216	0.440	19.6	0.19
Acute/chronic stressors	8	339	47	0.064	0.178	0.046	.50	0.298	0.296	0.21	0.60	0.28	0.14	−0.076	0.409	10.2	0.18
No. NK	21	638	20	**0.515**	**0.527**	0.488	.81	0.399	0.408	1.29	1.29	**<1.0E-35**	**5.0E-6**	0.370	0.654	188.7	1.9E-29
Hyperacute stressors	16	485	20	**0.637**	**0.651**	0.647	1	0.305	0.314	2.13	2.03	**<1.0E-35**	**4.0E-7**	0.523	0.729	79.8	7.6E-11
Acute/chronic stressors	5	153	22	−0.104	0.054	0.000	.20	0.288	0.273	−.361	0.200	0.95	0.69	−0.286	0.381	3.6	0.47
No. CD25	2	72	36	−0.195	−0.265	−0.248	.50	0.379	0.367	−0.52	−0.72	0.10	0.50	−0.999	0.997	4.5	0.03
No. HLA-DR	3	144	37	0.019	0.011	0.000	.33	0.021	0.019	0.90	0.58	0.39	0.41	−0.036	0.058	0.0	0.98
% B	6	86	12	0.216	0.288	0.121	.50	0.593	0.593	0.36	0.38	0.06	0.44	−0.449	0.739	21.5	0.0007
% CD3	10	385	20	**−0.175**	**−0.139**	−0.122	.70	0.152	0.148	−1.15	−0.94	**0.0008**	**0.02**	−0.242	−0.033	6.2	0.72
% CD4	22	810	28	**−0.075**	−0.126	−0.044	.55	0.334	0.381	−0.23	−0.37	**0.03**	0.11	−0.275	0.029	83.2	2.4E-9
% CD8	21	780	25	**−0.066**	−0.008	0.000	.43	0.277	0.277	−0.24	−0.03	**0.02**	0.90	−0.137	0.121	32.7	0.04
Hyperacute stressors	7	105	12	0.174	0.205	0.000	.43	0.292	0.312	0.60	0.66	0.09	0.14	−0.090	0.467	7.8	0.25
Acute/chronic stressors	14	675	44	**−0.099**	**−0.115**	−0.031	.57	0.189	0.196	−0.53	−0.59	**0.009**	**0.05**	−0.225	−0.001	19.3	0.11

% NK	8	301	33	**−0.131**	0.107	0.150	.38	0.531	0.522	−0.25	0.20	**0.002**	0.62	−0.360	0.531	55.0	1.5E-9
Hyperacute stressors	4	63	14	**0.532**	**0.517**	0.512	1	0.188	0.215	2.82	2.40	**2.6E-5**	**0.02**	0.220	0.726	1.4	0.70
Acute/chronic stressors	4	238	61	**−0.307**	−0.343	−0.254	.75	0.332	0.377	−0.92	−0.91	**2.1E-5**	0.17	−0.757	0.266	20.0	0.0002
CD4/CD8 ratio	21	738	38	**−0.194**	**−0.176**	−0.105	.56	0.333	0.332	−0.58	−0.53	**3.6E-13**	**0.006**	−0.079	−0.395	107.3	6.0E-14
Hyperacute stressors	10	417	31	**−0.462**	**−0.439**	−0.481	.90	0.329	0.344	−1.40	−1.28	**<1.0E-35**	**0.003**	−0.211	−0.622	35.6	4.6E-5
Acute/chronic stressors	11	469	40	−0.047	−0.038	0.000	.36	0.243	0.254	−0.16	−0.19	0.20	0.56	−0.218	0.127	28.9	0.002
Humoral factors																	
EBV Ab titers	6	316	57	**0.383**	**0.383**	0.348	.83	0.275	0.275	1.39	1.39	**6.1E-11**	**0.02**	0.107	0.604	12.5	0.03
HSV Ab titers	3	174	61	**0.364**	0.534	0.351	.67	0.391	0.391	0.93	1.37	**1.3E-5**	0.13	−0.405	0.925	18.6	9.0E-5
IgA	9	496	59	−0.037	−0.091	−0.013	.56	0.435	0.432	−0.08	−0.21	0.63	0.57	−0.419	0.258	86.8	2.1E-15
IgG	5	303	50	0.012	0.058	−0.018	.40	0.311	0.307	0.04	0.19	0.58	0.71	−0.324	0.424	19.6	0.0006
IgM	5	289	40	0.007	0.056	0.242	.60	0.384	0.380	0.02	0.15	0.63	0.77	−0.414	0.503	31.9	2.1E-06
Functional measures																	
NK cytotoxicity	18	649	28	**−0.189**	−0.066	−0.169	.61	0.483	0.483	−0.39	−0.14	**3.1E-6**	0.60	−0.317	0.193	106.5	5.6E-15
Hyperacute stressors	7	156	19	−0.042	0.214	0.417	.29	0.627	0.632	−0.07	0.34	0.88	0.47	−0.440	0.719	84.8	3.6E-16
Acute/chronic stressors	11	493	40	**−0.225**	**−0.242**	−0.270	.82	0.204	0.213	−1.10	−1.14	**2.3E-5**	**0.004**	−0.373	−0.102	17.9	0.06
PHA	23	901	30	**−0.186**	**−0.211**	−0.169	.70	0.260	0.264	−0.72	−0.80	**2.1E-6**	**0.001**	−0.320	−0.098	40.0	0.01
Con A	15	575	29	**−0.285**	**−0.411**	−0.441	.73	0.375	0.363	−0.76	−1.13	**2.8E-6**	**0.0006**	−0.570	−0.221	78.5	5.4E-11
PWM	7	313	29	−0.159	**−0.272**	−0.334	.57	0.307	0.282	−0.52	−0.97	0.08	**0.04**	−0.498	−0.011	18.8	0.005
IFN production following stimulation	3	109	40	**−0.493**	−0.608	−0.431	1	0.489	0.458	−1.01	−1.33	**9.2E-5**	0.13	−0.959	0.480	24.9	4.0E-6
% CD25 following stimulation	3	66	22	**−0.656**	**−0.655**	−0.706	1	0.216	0.216	−3.03	−3.03	**8.5E-8**	**0.03**	−0.869	−0.234	2.0	0.37
Leukocyte adhesives	3	517	169	**0.452**	**0.435**	0.457	1	0.055	0.048	8.23	9.06	**<1.0E-35**	**0.004**	0.333	0.527	0.3	0.88

Note. Effect sizes which differ reliably from zero ($p < .05$) are shown in bold with their respective probability levels. See Table 1 for glossary.

TABLE 4
Random Effects of Moderator Analyses in Studies of Stressors

Moderator variable	Immune measure	Number study groups	Spearman *r*	Two-tailed $p <$
Subject characteristics				
Sex (% female)	# lymphocytes	18	.46	.05
	# CD3	18	.78	.001
	# CD4	26	.65	.001
Age	# CD4	26	.51	.01
Study characteristics				
Temporal duration (1 = hyperacute; 0 = other)	# NK	21	.72	.001
	% NK	8	.91	.01
	% CD8	21	.43	.05
	CD4/CD8	21	−.72	.001
Nature of stressor (1 = experimental; 0 = naturally occurring)	# NK	21	.56	.01
	% NK	8	.91	.01
	% CD8	21	.43	.05
	CD4/CD8	21	−.72	.001
Source of information (self-report vs objective)	None			

trast, the random-effect approach, though generally less powerful, permits generalization to other studies from the same population from which the studies included in the review were sampled. Furthermore, random-effect analyses explicitly take variable findings between studies into account when predicting the range of effect sizes likely to be seen in future studies. Finally, the present review is the first to include statistical evaluations of heterogeneity and moderator effects.

Depression and Immunity

Depression's relation to immunological assays is complex and, for many parameters, significantly variable. Though 30 of 39 immune measures (77%) were significantly associated with depression under fixed-effect analyses, heterogeneous findings predominated. Not surprisingly, fewer [11 of 39 relations (28%)] were significant under random-effects analyses based on the number of studies rather than the number of subjects. By random-effect analyses, future studies of depressed patients are very likely to observe (1) a lymphopenia and relative neutrophilia; (2) an increased CD4/CD8 ratio, (3) increased circulating haptoglobin, sIL-6, and PGE_2 levels; (4) reduced NK cell cytotoxicity; and (5) reduced lymphocyte proliferative response to mitogen. Additionally, under the fixed-effect analysis, accumulated subjects reliably exhibited a relative monocytopenia (albeit in the context of a marginal *absolute* monocytosis); an absolute decrease in NK-cell levels and relative decrease in T-cell levels; increased levels of cells bearing activation markers (i.e., CD25 and HLA-DR); increased positive acute phase plasma protein (APP) levels, including α1-acid glycoprotein and α1-antitrypsin; decreased negative acute phase plasma protein levels, specifically albumin; and increased serum circulating soluble IL-2 receptors (sIL-2r). However, the latter set of findings are too preliminary to indicate that future studies will obtain similar results. Thus, major depression *may* be associated with immune activation reminiscent of an acute phase response and is reliably associated with impairments in NK- and T-cell-mediated functions.

Previous fixed-effect meta-analytic reviews (Herbert & Cohen, 1993a) suggested that elderly and hospitalized patients showed more pronounced alterations than young or ambulatory depressives and that these differences pervaded across most immune measures. Our results, which are based on many more studies and rely on the more generalizable random effect approach, differ in part. The five moderator variables that were examined only partially explained the enormous heterogeneity observed. None was a significant moderator of more than three relations under the random-effect model. Therefore, much of the heterogeneity was due to other factors. These results point to the need for further exploration of other moderators of the relation of depression to immunity (e.g., presence of melancholic/vegetative symptoms, comorbidity, time/season of sampling, and responsiveness to treatment). In addition, follow-up studies and random-effect meta-analytic reviews with more power should further examine the role of the moderators we have identified.

Our review and that of Herbert and Cohen (1993a) observed similar relations between depression and many immune measures. Thus, both reviews report a lymphopenia and neutrophilia, reduced NK-cell levels and cytotoxicity, and reduced lymphocyte proliferative response to mitogen. However, conflicting results were obtained for several measures. In contrast to their findings, we observed a relative monocytopenia rather than a monocytosis across accumulated subjects (although a reliable, but very small, *absolute* monocytosis is evident in our accumulated studies). Furthermore, we did not observe consistent changes in the *absolute* number of circulating B or T cells, nor in the helper/inducer (CD4) or suppressor/cytotoxic (CD8) subsets. In contrast, Herbert and Cohen (1993a) reported significant decrements in each of these cell subsets. In fact, we observed *proportional increases* in B-cell and CD4 populations (albeit in the face of a relative decrease in T-cell populations). Furthermore, we observed increased CD4/CD8 ratios across accumulated subjects, whereas they reported reductions. Finally, in our review, significant relations were consistently smaller in magnitude. These differences may be due to several factors. First, more studies were available for our review. For the discrepant measures, our review examined two to six times more studies. This reduces the file-drawer issue and, therefore, the chance of observing spurious relations (Rosenthal, 1991). Herbert and Cohen (1993a) reported that the file-drawer issue was not a concern for many of these relations. However, their calculations of a fail-safe *N* were based on a fixed-effect model that is likely to result in a large fail-safe model. More generally, a larger sample of studies and subjects may provide a more reliable estimate of the true relation of depression to the immune measures.

A second possible source of discrepancies is that newer studies may differ systematically on important moderator variables from studies included in their review. For example, consistent differences in the samples' sex ratio or severity of depression as well as the adequacy of age and sex matching of controls might contribute to discrepancies in the numerical B- and T-cell measures. Follow-up studies can determine whether such differences account for variable relations between depression and B- and T-lymphocyte counts.

Stressors and Immunological Assays

As with depression and immunological assays, the relationship between stressors and immunological assays is complicated and, for many parameters, significantly variable. Though 19 of 32 immune measures (59%) were significantly associated with various stressors under fixed-effect analyses, heterogeneous findings predominated.

Because of the decrease in power, fewer relations (12 of 32, or 37%) were significant under random-effect analyses. Future studies of stressed subjects (as determined by random-effects analyses) are likely to find the following: (1) an absolute lymphocytosis; (2) an absolute expansion of cytotoxic lymphocyte subsets (NK or CD8), manifesting as a relative reduction of T lymphocytes and the CD4/CD8 ratio; (3) increased EBV antibody titers; (4) reduced T-cell proliferative response and proportions of IL-2r-bearing cells following mitogenic stimulation; and (5) increased leukocyte adhesiveness.

Once again, a significant degree of heterogeneity was found for most immune measures. For measures related to cytotoxic lymphocytes, the heterogeneity was, in part, a function of the study design. Thus, experimental, hyperacute stressors reliably increased circulating levels of cells bearing cytotoxic lymphocyte markers (i.e., CD16, CD56, or CD8). In contrast, studies of naturally occurring, acute/chronic stressors consistently observed decreases in these cell populations as well as in NK cytotoxicity. Possibly a consequence of this, the former category of studies observed reduced CD4/CD8 ratios, whereas the latter found increased or unaltered CD4/CD8 ratios. Other research (Brosschot et al., 1992; Schedlowski, Jacobs, Alker, & Prohl, 1993; Schedlowski, Jacobs, Stratmann, et al., 1993) suggests that this pattern represents a biphasic, cell-trafficking response rather than a change resulting from sustained exposure to stressors. This pattern also appears to be true of NK cytotoxicity (Brosschot et al., 1992; Kappel et al., 1991), though we were unable to demonstrate it to a statistical certainty, possibly because of low power. This difference between studies of experimental, hyperacute stressors and studies of naturalistic, nonhyperacute stressors also seems to explain the apparent discrepancy between our findings for relative and absolute CD8 levels. That is, a much greater proportion of studies of CD8 counts utilized experimental or hyperacute stressors, whereas a greater proportion of studies of relative CD8 levels utilized other stressors. When these studies are separated by these distinctions, results are quite comparable across both measures. Thus, the initial response to stressors may be a demargination of cytotoxic lymphocytes, with a concomitant increase in circulating counts and lytic activity. Within a few hours, however, cytotoxic lymphocyte counts and activity are significantly reduced, accompanied by an increased CD4/CD8 ratio.

Again, our fixed effect review and Herbert and Cohen's (1993b) fixed-effect review of stressor studies generated similar findings on many measures. Both reviews observed the following stress-related changes: leukocytosis, reduced CD4 counts, increased HSV antibody titers, and reductions in T-cell proliferative response to mitogen. Furthermore, both suggest a biphasic response of circulating cytotoxic lymphocyte levels and lytic activity to stressors. Differences observed between the two reviews, such as findings for NK cells and CD4/CD8 ratios, probably reflect the different types of studies included in each review—our review had proportionally more studies of hyperacute, laboratory-induced stressors.

Comparison of Depression and Stressor Findings

Utilizing results from both fixed- and random-effect analyses, both depression and stressors have been reliably associated with an absolute leukocytosis, a relative reduction in T-cell populations and lowered lymphocyte proliferative response to mitogen. Additionally, both depression and acute/chronic stressors have been reliably related to reduced NK-cell levels and lytic activity as well as increased CD4/CD8 ratios.

TABLE 5
Summary of Expected Immunological Correlates of Depression and Stressors

Measure	Weighted *r*	Unweighted *r*
Depression		
↑ Leukocytes	.19*	.27*
↓ % lymphocytes	−.48*	−.22*
↑ % neutrophils	.54*	.32*
↑ CD4/CD8 ratio	.19*	.17*
↑ Haptoglobin	.45*	.50*
↑ PGE_2	.52*	.54*
↑ IL-6	.37*	.35*
↓ NK cytotoxicity	−.35*	−.34*
↓ Lymphocyte proliferative response to mitogen (PWM, Con A, and PHA)	−.21−−.26*	−.31−−.34*
Stressors		
↑ Leukocytes	.14*	.17*
↑ # lymphocytes	.09	.19*
↓ % CD3 (T cells)	−.18*	−.14*
↑ EBV antibody titers	.38*	.38*
↓ Lymphocyte proliferative response to mitogen (PMW, Con A, and PHA)	−.16−−.29*	−.21−−.41*
↓ % IL-2r bearing cells following mitogenesis	−.66*	−.66*
↑ Leukocyte adhesiveness	.45*	.44*
Hyperacute stressors		
↑ # CD8 (suppressor/cytotoxic lymphocytes)	.27*	.33*
↑ # NK (natural killer lymphocytes)	.64*	.65*
↑ % NK	.53*	.52*
↓ CD4/CD8 ratio	−.46*	−.44*
Acute chronic stressors		
↓ % CD8	−.10*	−.11*
↓ NK cytotoxicity	−.23*	−.24*

* $p < .05$ differs from 0.

However, for both depression and stressors, variable findings are the rule, not the exception. Under the more generalizable random-effect model, only three differences—leukocytosis, reduced blastogenic response to PHA, and reduced NK cell cytotoxicity—are very likely to be observed in relation to both depression and acute/chronic stressors.

Some immune alterations may discriminate stressed and depressed individuals. Opposite relations have been reliably observed for lymphocyte counts (increased by stress and decreased in depression). Furthermore, preliminary findings indicate that depressed patients display an excess of circulating IL2r-bearing cells, whereas no such stressor-related excesses are reliably observed. Finally, there is some suggestion that immunologic differences may be larger in depressed patients than in stressed individuals (see Table 5). Future work should attempt to reproduce these differences within a single study design and determine their possible pathophysiologic significance.

One factor to consider when interpreting nonsignificant results obtained under random-effect analyses is the available statistical power. Clearly, some homogeneous

relations that were significant under fixed-effect analysis are unlikely to be revealed under a random-effect model simply because of the paucity of studies (e.g., depression and $CD25^+$ lymphocytes). For relations that involve few studies, an alternative, descriptive metric to consider is the coefficient of robustness (CR), which explicitly takes variable findings into account. Because no published standards exist, we used one that is suggested by the present review: CRs of an absolute magnitude greater than 1 are moderate to large (the effect size being at least as large as its associated standard deviation). For depression, this standard suggests that the following findings are the most robust of those reviewed: (1) a relative lymphopenia and neutrophilia, (2) increased numbers of circulating lymphocytes bearing activation markers, (3) increased levels of positive acute phase proteins and decreased levels of negative acute phase proteins, (4) altered immunoglobulin levels (increased IgM and decreased IgG), (5) increased circulating prostaglandin and IL-6 levels, and (7) decreased NK cytotoxicity. In stressors, the most robust findings have been (1) changes in cytotoxic lymphocyte levels, lytic activity, and CD4/CD8 ratios, with the direction of change depending on stressor chronicity; (2) a relative decrease in circulating T cells; (3) increased antibodies to Epstein–Barr virus (EBV); (4) decreased proportions of IL2r positive cells and production of interferon (IFN) following mitogenic stimulation; and (5) increased leukocyte adhesiveness. Future studies should attempt to replicate those findings that are robust, but preliminary. Indeed, with a sufficient number of studies ($k = 21$), a relation of only moderate robustness—the leukocytosis associated with stressors (CR's = 0.5–0.7)—was shown to be reliably expected in future studies.

Unique Features of the Meta-Analysis

The meta-analytic approach in this study is unique in some respects. The presentation included (a) two effect size measures (weighted and unweighted *r*'s), (b) two measures of the consistency of findings (coefficient of robustness and heterogeneity tests), and (c) two tests of significance (fixed effect and random effect). This comprehensive approach recognizes the complexity of the meta-analytic task and the need to consider issues such as effect size, statistical significance, and consistency of findings from different perspectives. We have attempted to specify which question each of these data presentations is designed to address rather than rank the various presentations according to their purported validity or ''correctness.''

CONCLUSION

The present article updates and extends Herbert and Cohen's (1993a, 1993b) earlier efforts to quantify the relations of depression and stressors to immunological assays. Our review indicates that statistically reliable immunologic differences exist in depressed and stressed individuals, as was the case at the time of previous reviews (Herbert & Cohen, 1993a, 1993b; Stein et al., 1991; Weisse, 1992). Also of note, we observed interlaboratory reproducibility for these findings, whereby *at least* two independent laboratories obtained results consistent with the overall significant effect (data not shown). Nevertheless, *the clinical significance of these variations for a person's health* remains largely unknown. This type of significance is briefly considered here: reduced NK cytotoxicity is associated with increased morbidity for many diseases, including cancer and infectious disease (Whiteside, 1990) and has been suggested to be a risk factor for accelerated HIV progression (see Evans et al., 1995

for a review). Furthermore, lowered lymphocyte proliferative responsiveness is associated with increased numbers of hospitalizations and mortality in the elderly (Murasko, 1990; Murasko, 1988) and accelerated HIV progression (Murray et al., 1985). However, these prognostic relations might be irrelevant to the typical impact of psychosocially related immunologic differences on disease. The differences observed in prognostic studies were much larger; were lifelong (Whiteside, 1990); might be consequent to, rather than the cause of, deteriorating health (Murasko, 1988, 1990; Murray et al., 1985); and might be specific to the elderly (Murasko, 1988, 1990). More to the point, neither depressive symptoms nor stressors per se have been linked to accelerated HIV progression (Zorrilla, McKay, Luborsky, & Schmidt, 1996).

Nevertheless, evidence has linked stressors and/or depression to increased susceptibility to the common cold and upper respiratory infections (Cohen, 1991, 1996; Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991), increased clinical recurrence of HSV (Zorrilla et al., 1996), and marginally increased cancer morbidity (McGee, Williams, & Elwood, 1994). Results from one such study (Linkins & Comstock, 1990; Covey, Glassman, & Dalack, 1991), however, suggest that at least one of these disease relations may be attributed more parsimoniously to behavioral, rather than immunologic, differences. To date, no human study has demonstrated through path analyses or related mediational strategies (Baron & Kenny, 1986) that psychoimmunologic differences are responsible for psychodisease relations. Moreover, no human studies have demonstrated that the magnitude of immunologic differences revealed in the present review have significant deleterious effects on a person's health, although experimental animal research is suggestive. More work is needed to show the degree to which the immunological alterations seen in depressed and stressed people have clinical relevance.

Although the clinical significance of the alterations in immune measures that are associated with depression and stressors is not clear, comparing our results with those obtained in meta-analyses of research in other fields can at least provide an indication of the relative size of the effects we observed. In our meta-analysis, the absolute values of the effect sizes for the immune variables that were significant under the random effect analyses ranged from $r = .17$ to $r = .54$ in the depression studies and from $r = .11$ to $r = .66$ in the stressor studies. According to conventions established by Cohen (1992), these results were indicative of small to large effects for both depression and stressors. By way of comparison, Lipsey and Wilson (1993) recently conducted a meta-analysis of results from 302 meta-analyses of psychological, educational, and behavioral treatment interventions. The overall effect size from these meta-analyses was $d = .50$, which is equivalent to $r = .24$. According to Cohen (1992), this represents a medium effect and is typically considered clinically significant. Lipsey and Wilson (1993) also summarized meta-analyses that had been done for various medical treatments (e.g., aortocoronary bypass surgery, chemotherapy for breast cancer, drug treatments for arthritis, and drug treatments for behavioral disorders). These studies yielded effects sizes that typically ranged from $r = .05$ to $r = .43$. These comparisons indicate that the effects we observed with some of the immune measures are relatively large in comparison to effects observed in other areas of psychological and medical research.

Finally, an accumulating set of findings synthesized in the present meta-analysis suggest that major depression, but not stressors, is associated with immune activation

reminiscent of an acute phase response. Most previous speculation has focused on the possibility that depression increases susceptibility to diseases that opportunistically exploit reductions in specific and natural immunity. Evidence for a macrophage-mediated inflammatory process suggests that future research should more closely examine the risk for and progression of autoimmune disorders and hypersensitivity disorders in depressed patients (Kagan, Snidman, Julia-Sellers, & Johnson, 1991; Parker, Smarr, Angelone, & Mothersead, 1992).

Future research should replicate the preliminary findings that indicate an inflammatory process in depression. Maes and colleagues have argued that macrophage activation, with concomitant monokine release, is involved in depression's inflammatory response (Maes, 1995; Maes, Smith, & Sharpe, 1995). In rats, exposure to uncontrollable shock, a putative animal model of depression, increases CD4/CD8 ratios and produces impairments in T-cell-mediated proliferation that depend on activated macrophages (Fleshner, Bellgrau, Watkins, Laudenslager, & Maier, 1995). The close correspondence of these experimental findings to those obtained in our review of studies of depressed patients is striking. It suggests that the impairments in T- and NK-cell-mediated functions observed in depressed patients may be secondary to macrophage activation, which also likely contributes to their apparent acute phase response.

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