Interpersonal Stress, Depression, and Disease Activity in Rheumatoid Arthritis and Osteoarthritis Patients

Alex J. Zautra, Mary H. Burleson, Kathy S. Matt, Sanford Roth, and Lisa Burrows

The relationships among interpersonal stressors, depression, coping inefficacy, hormones (prolactin, cortisol, and estradiol), and disease activity were examined. The sample comprised 33 women with rheumatoid arthritis (RAs; age 37-78) and 37 women with osteoarthritis (OAs; age 47-91), who served as controls. In a regression analysis, interpersonal conflict events accounted for more than twice as much variance in depression in RAs than in OAs. In the RA patients, the immune-stimulating hormones prolactin and estradiol were significantly positively correlated with interpersonal conflicts, depression, coping inefficacy, and clinician ratings of disease activity, suggesting that RAs are more reactive to interpersonal stressors than are OAs, both psychologically and physiologically.

Key words: interpersonal stress, arthritis, depression, hormones

Both life stress and psychological adjustment are thought to play important roles in illness resistance and disease course for those who become ill (Borysenko & Borysenko, 1982; Hinkle, 1974; Kiecolt-Glaser et al., 1987; Locke, 1982; Rahe, 1974). Rheumatoid arthritis (RA) patients—who must cope with functional loss and recurrent, painful flare-ups from a chronic disease—may be among the most vulnerable to the disruptive effects of life stress (Depue & Monroe, 1986). Indeed, there are few illnesses potentially more debilitating than RA (Anderson, Bradley, Young, McDaniel, & Wise, 1985). In its active stages, the disease is characterized by unpredictable episodes of extreme pain and disability, against a background of chronic impairment. Because of the strain placed on their capacity to adjust psychologically, both from the illness itself and also from related psychosocial stresses, RA patients may be at great risk for collapse of their physical health. A vicious cycle of illness, stress, and illness recurrence may become established (Solomon, 1981). This study examines the effect of everyday stress on the mental and physical health of arthritis patients.

There has been considerable conjecture on the role of psychosocial stress in provoking flare-ups and disease progression in RA. Stress is the cause most often given by RA patients for their flare-ups (Affleck, Pfeiffer, Tennen, & Fifield, 1987). Nevertheless, few studies have supported a direct link between life stress and illness course in human RA subjects (cf. Hendrie, Paraskevas, Baragar, & Adamson, 1971; Zautra et al., 1989). Barriers to the demonstration of such effects may be found in shortcomings of measurement and methods on both sides of the stress and illness equation.

The complexity of assessing and distinguishing among the many components of the life stress process has been a formidable obstacle. In fact, reliance on inadequate measurement instruments may have led researchers to dismiss prematurely the role of stress in physical illness in studies where no significant effects of stress on health were observed (e.g., Schroeder & Costa, 1984). On the other side of the equation, few have attempted to identify specific neuroendocrine and immune parameters likely to mediate the effects of stress on disease activity in RA. These shortcomings have left major gaps in our understanding of the processes responsible for the observed effects of life stress on the course of RA.

Psychosocial Stress and Rheumatoid Arthritis

Recently, advances have been made in the measurement of everyday life events that may add precision to the detection of changes in life stress associated with illness. Unlike major events, which occur infrequently, these small stressors fluctuate widely over short periods of time, resulting in meaningful differences between subjects across days and weeks (Tennen, Suls, & Affleck, 1991). Thus, they provide a potentially better method for testing the effects of life stress in illnesses such as RA, where disease flare-ups can occur and recur in a single month.

Several investigators have suggested a vulnerability model in which small chronic stressors would play an important role in disease progression. In this model, the occurrence of smaller, everyday events in sufficient quantities may place enough additional stress on a person already weakened from chronic illness to precipitate an illness episode (Depue & Monroe, 1986; Kessler, Price, & Wortman, 1985; Zautra, Guarinacci, & Dohrenwend, 1986). Initial research has found support for this vulnerability model by showing that everyday stressors are associated with illness susceptibility (Delongis, Folkman, & Lazarus, 1988; Stone, Cox, Valdimarsdottir, Jandorf, & Neale,
1987). However, research has yet to address the strength of the association between everyday stress and illness, to identify which stressors are the most salient, or to determine which patient groups are the most vulnerable.

There are many types of everyday stressors, and some forms of stress are more likely to be associated with distress and disruption of internal homeostasis than others. In a diary study of married couples, Bolger, Delongis, Kessler, and Schilling (1989) found that daily interpersonal stressors were, by far, the most distressing events. Among the chronically ill, ongoing strains from a troubled marriage and other interpersonal tensions may be especially likely to cause increased psychological and biological disturbance. For example, family conflict has been associated with poor adjustment to chronic illness (Coyne, Wortman, & Lehman, 1988), as well as to immune system dysfunction (e.g., Kiecolt-Glaser et al., 1987).

There is reason to suspect that RA patients may be especially sensitive to interpersonal conflict events. They are at risk for severe disability and are therefore dependent on the maintenance of ties with caregivers, even when those relationships are troubled (Manne & Zautra, 1989). In fact, poor psychological adjustment to RA has been associated with troubled family relations (Manne & Zautra, 1989; Shochet et al., 1969).

In addition to the stress-to-illness hypothesis, depression is also important to examine. Not only are mental health outcomes significant in their own right, but the patient's psychological condition may also play a pivotal role in disease progression. From a biobehavioral perspective, the level of depressive symptoms may provide one of the best measures of mental health. Patients with chronic illness and in pain are likely to report many more depressive symptoms (Haythornthwaite, Sieber, & Kerns, 1991). Furthermore, stressful inter-personal environments are known to increase the frequency of depressive symptoms in both healthy and ill groups (Finch & Zautra, 1992). Depression has also been associated with endocrine changes (Heninger, Charney, & Sternberg, 1984; Miyabo, Asato, & Mizushima, 1977; Miyabo, Hisado, Asato, Mizushima, & Ueno, 1976) and lymphocyte regulatory dysfunction (Kronfol et al., 1983; Schleifer, Keller, Siris, Davis, & Stein, 1985; Weisse, 1992). Indeed, the demoralization and feelings of helplessness that accompany depression may be a critical risk factor in further exacerbations of RA.

Negative self-evaluation of coping efficacy is another factor related to both depression and life stress (Aldwin & Revenson, 1988; Lorig, Chastain, Ung, Shoor, & Holman, 1989; Schiaffino & Revenson, 1992; Zautra & Wrabetz, 1991). Depressed patients are likely to undervalue their capacity to cope effectively with disease and other stressful events. By doing so, they may increase their risk of further illness exacerbations, thus contributing to the vicious cycle of stress and disease progression. Consistent with this argument, perceived inability to cope with future stressors has been associated with poorer mental health and higher circulating B-cell proportions in RA patients in past studies (e.g., Zautra et al., 1989).

Physiological Mediators

To provide a comprehensive model of the effects of psychosocial stressors on health, it is important to understand how these external signals exert their influence by changing internal messages such as hormonal signals, which then alter the internal physiological state. Much past research on stress has focused on the hypothalamic–pituitary–adrenal axis and its role in immune function (Selye, 1956). Stress, including social stress (Meyerhoff, Oleshansky, & Mouey, 1988), affects the central nervous system, causing the eventual release of prolactin (PRL) and adrenal corticotropic hormone (ACTH) from the pituitary gland and cortisol from the adrenal cortex (Euker, Meites, & Riegel, 1975; Matt, Soares, Talamanes, & Bartke, 1983; Neill, 1970; Plotisky, 1991). In the healthy individual, cortisol suppresses cellular immune function (thus reducing inflammation; Cohen & Crnic, 1982), whereas PRL is stimulatory (Russell, 1989). These opposing actions, as well as the action of gonadal steroids, allow for modulation of the immune response around a homeostatic set point.

However, because RA is a systemic autoimmune disorder, the homeostatic mechanisms that normally regulate immunity and inflammation may not be fully functional (Dorian & Garfinkel, 1987). Dysregulation in this system suggests that RAs might be especially hormonally responsive to psychosocial stress, possibly leading to increased immune system activity and disease flare-ups. Immune activation in RA may also be augmented through other immune-stimulating hormones, such as estrogen. Estrogen is associated with increased autoantibody production (Ahmed, Dauphinee, Montoya, & Talal, 1989) and also stimulates PRL release (Wiedmann, Schwartz, & Frantz, 1976). Risk of RA is three times greater in women than in men, and autoimmune disease activity is known to increase in the presence of estradiol (McGregor, 1990)—features consistent with the role of estrogen in the autoimmune response. In summary, even though many factors besides stress regulate adrenal and gonadal steroid hormone release (Spector, 1989), we thought it would be useful to examine circulating levels of PRL, cortisol, and estradiol (estrogen), because these hormones could mediate the effects of stress and depression on the immune system and disease activity in RA.

We designed the study to explore the effects of interpersonal stresses on depression and disease state in RA patients in treatment for their disease. Blood samples were collected and analyzed for serum levels of PRL, cortisol, and estradiol. Patients with osteoarthritis (OA) in treatment were used as controls; these patients were expected to experience a moderate degree of pain and discomfort, like the RAs, because they were seeking treatment. However, OAs differ from RAs in that they have a localized joint pain from cartilage damage, not from an immune-related inflammation such as occurs with RA. The diseases differ in clinical course as well as physiopathology. RA can be crippling and is progressive in its effects leading to erosion in the bone itself, whereas osteoarthritis has a much more benign clinical course (Lorig & Fries, 1990).

There was good reason to believe, therefore, that the RAs and OAs would be similar in immediate concerns due to pain and discomfort but that the RAs might be especially hormonally responsive to psychosocial stress, possibly leading to increased immune system activity and disease flare-ups. Immune activation in RA may also be augmented through other immune-stimulating hormones, such as estrogen. Estrogen is associated with increased autoantibody production (Ahmed, Dauphinee, Montoya, & Talal, 1989), and also stimulates PRL release (Wiedmann, Schwartz, & Frantz, 1976). Risk of RA is three times greater in women than in men, and autoimmune disease activity is known to increase in the presence of estradiol (McGregor, 1990)—features consistent with the role of estrogen in the autoimmune response. In summary, even though many factors besides stress regulate adrenal and gonadal steroid hormone release (Spector, 1989), we thought it would be useful to examine circulating levels of PRL, cortisol, and estradiol (estrogen), because these hormones could mediate the effects of stress and depression on the immune system and disease activity in RA.

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Method

Participants

Participants were 33 female RA patients and 37 female OA patients, who routinely came to an arthritis clinic for monthly blood tests to monitor their medication. Ninety percent of the participants were White, 3% were African American, and 7% were Hispanic. Approximately 73% of the RA patients were married, 6% were single, 6% had been widowed, and 15% were divorced. Among the OA patients, 60% were married, 5% were single, 24% had been widowed, and 11% were divorced. Eighty-eight percent of the RAs and 86% of the OAs had completed high school or beyond.

The RA patients were recruited from a list, prepared by the clinic staff, of all female RA patients treated at the clinic. All were diagnosed as having either classical or definite RA (Rodnan & Schumacher, 1983). The OA patients were recruited from among the female patients diagnosed with OA visiting the clinic on the same days that the RA participants were interviewed. Approximately one third of the patients who were asked to participate in the study declined. Approximately equal numbers of RAs and OAs refused to participate in the study.

Procedure

Patients were approached in the waiting room of the arthritis clinic at the time of their regularly scheduled appointments and asked if they wished to participate in the study. If the patient agreed to participate, she signed an informed-consent statement and was paid $10. She was then taken to a private room, in which a structured interview was conducted. The interview included questions concerning demographic information, length of diagnosis with the disease, joint tenderness and swelling, amount of arthritis pain the patient was currently experiencing, and activity limitation. Additionally, patients were asked to report recent desirable and undesirable non-arthritis-related life and health events, interpersonal stressors, and positive interpersonal events. Coping efficacy for arthritis flare-ups and recent interpersonal stressors was also assessed. Patients then filled out a packet that contained measures of depression, psychological distress, and mood.

The structured interviews were suspended, if necessary, in order for a physician or a nurse practitioner at the arthritis clinic to examine the patient. Physicians' joint assessments and global ratings of arthritis activity were obtained at this time. The interviews were resumed on completion of the clinician's examination. If the patient was unable to stay at the clinic for the full interview, it was completed over the telephone as soon as possible. Fifteen percent of the interviews were finished over the telephone on the same day as the patient's visit to the clinic, and 5% were completed the following day.

Information on medications that the patient was currently taking was obtained from the patient's medical records. Nursing staff at the arthritis clinic routinely verified medication use with each patient at the time of their visit to the clinic. Thus, this information was accurate and up-to-date.

Nursing staff at the arthritis clinic were alerted to draw 10 ml beyond what was needed for the clinic's analysis. The blood was delivered to the project biochemist for analysis.

Measures

Events. In this study, everyday desirable and undesirable events were measured with the Inventory of Small Life Events (Zautra et al., 1983). This inventory was constructed to minimize confounding with personality dispositions or affective states while preserving established criteria for what constitutes a life event. All items on the list were written to have a discrete beginning, to be scorable as desirable or undesirable (by a consensus of 80% or higher), and to refer to observable changes in everyday activities rather than internal states.

Participants reported whether each event happened in the past week or past month and whether its occurrence was related to their arthritis condition. They rated 144 small events (e.g., "got a traffic ticket," "had a party"). These events were further subdivided into desirable, undesirable, and ambiguous-desirability event categories. The events covered 13 different areas of life—including marital relations, children, extended family, social relations, recreation, school, work, finances, and health events.

It was expected that interpersonal events would be the most salient for the patients. Therefore, the analyses focused on these events. Small events with interpersonal content were summed across categories of marital relations, children, extended family, social relations, and recreation. Two scores were constructed from these summations: one for interpersonal conflict events and one for positive interpersonal events. Noninterpersonal stressors were also examined for their correlations with depression, to check on our assumption that the interpersonal events were the most salient for this population.

To reduce a possible confounding with illness-related stressors, events that the subject reported could be attributed, at least in part, to their arthritis condition were not scored. Non-arthritis-related health symptoms were summed separately and were used in the analyses.

Coping inefficacy. Efficacy in coping with both nonarthritis events and arthritis flare-ups was also assessed, following the method used by Lennox, Dohrenwend, Zautra, and Marbach (1990), Zautra et al. (1989), and Zautra and Wraebert (1991). The patients were asked to select two stressful events from those that had occurred during the past month: the most stressful non-arthritis-related event and their most recent arthritis flare-up. They then answered 10 questions concerning their responses to the event, such as whether they attempted to "relax and forget about what happened," or to "do something to prevent a future recurrence." Immediately following the inquiry about specific coping responses, the interviewer asked the patient to answer two questions using 7-point scales: (a) "How satisfied are you with how you responded to the event," and (b) "If an event like this one were to happen in the future, how certain are you that you would be able to adjust well to its negative aspects?" Coping inefficacy was computed as the mean of scores on these two items separately for arthritis and nonarthritis stressors. Thus, coping inefficacy ratings were grounded in specific coping responses made to the events and expectations about similar future events. The alpha reliability coefficients for coping inefficacy for the non-arthritis-related stressful event and the flare-up were .48 and .64, respectively. Three subjects (2 RAs) reported no negative events independent of arthritis and, therefore, did not have scores on coping with non-arthritis-related events.

Depression. The 10-item Depression subscale from the Mental Health Inventory (Veit & Ware, 1983) was used to measure this variable. Participants used a 6-point scale to respond to items such as the following: "How much of the time have you felt lonely," "How often did you feel nothing turned out the way you wanted it to," and "How much of the time have you been in low or very low spirits?" The mean across 10 items constituted the score on depression used in the analyses. Past research has shown this measure to be internally consistent and stable over time and to accurately assess individual differences in psychological distress among RA patients and older adults in general (Manne & Zautra, 1989; Zautra, Reich & Guaragna, 1988). In this study, an alpha reliability coefficient of .91 was obtained.

Self-reports of disability and pain. The Health Assessment Questionnaire (HAQ) from Fries, Spitz, Kraines, and Holman (1980) was used to measure the degree to which participants experienced arthritis-related activity limitation during the 7-day period before their visit to the arthritis center. This is a 20-item, self-report instrument in which the subject uses a 4-point scale to rate the amount of difficulty she experiences when performing various daily tasks. The subject is asked...
to assess her ability to perform daily tasks related to dressing and
goressing, arising, eating, walking, hygiene, household chores, and
reaching and gripping household objects. The mean score for the 20
items was computed. An alpha reliability coefficient of .93 was
obtained for this measure.

Patients were also asked to rate the amount of pain they were
currently experiencing by means of a visual analogue scale ranging
from no pain (0) to pain as bad as it could be (100). The number of years
since the patient had been diagnosed with her disease was also asked
of the patient and corroborated with medical records.

Clinical ratings of disease activity. Physicians and nurse practition-
ers used an abbreviated version of the American Rheumatism Associa-
tion Medical Information System (ARAMIS) Joint Count (Fries &
McShane, 1984) to assess the number of joints currently affected by
disease activity and the amount of disease activity in each joint.
Previous studies have shown abbreviated versions of this measure to be
valid and reliable (Fuchs, Brooks, Callahan, & Pincus, 1989). The
following 28 joints on the right and left sides of the body were included
in the assessment: distal interphalangeal (fingers), proximal inter-
phalangeal (fingers), metacarpophalangeal (first knuckle), carpometacar-
pals, wrists, elbows, shoulders, sternoclaviculars, temporomandibulars
(jaws), hips, knees, ankles, metatarsophalangeals (first foot knuckles),
and proximal interphalangeal (toes). Current disease activity in each
of these joints was rated on a scale ranging from 0 to 3. Ratings of
disease activity for each joint were summed to obtain a count of the
number of affected joints weighted by disease activity (weighted joint
count). Clinicians also made a global assessment of current disease
activity by means of a 4-point scale ranging from no disease activity (0)
to severe disease activity (3).

Hormone measurement. Blood was drawn from patients as previ-
ously described, and the serum was stored at -50°C until the time of
assay. Levels of PRL, cortisol, and estradiol were measured by
radioimmunoassay with kits purchased from ICN Biomedicals, Inc.
Samples were all measured in duplicate. Serum PRL was measured
with a double antibody precipitation assay, and values are expressed in
ng/ml. The intra-assay coefficient of variation (CV) was 6.9%. Serum
cortisol was measured directly in serum, using the coated tube assay
procedure of ICN Biomedical, Inc., and values are expressed as μg/dl; the
intra-assay CV was 9.6%. Serum estradiol was measured directly in
the serum, using a double antibody precipitation assay, and all values
are expressed as ng/ml. The intra-assay CV was 11.3%. All of the
sample values fell within the following normal ranges: cortisol (morn-
ing), 7–24 μg/dl; cortisol (afternoon), 3–11 μg/dl; PRL, 8–24 ng/ml;
estradiol (postmenopausal), less than 0.03 ng/ml.

Because of problems in drawing and transporting blood samples to
the laboratory where analyses were performed, full hormone data
were available for only 22 of the 33 RA subjects and 28 of the 37 OAs.
Therefore, the analyses reported for the psychosocial data alone have
a larger sample size than the analyses that included endocrine data.
However, the psychological results were also confirmed on the smaller
sample of subjects, for whom there was full data on hormone levels.

Results

Preliminary analyses were conducted for group differences in
demographic variables and illness severity. The OA and RA
groups did not differ in marital status or education. However, the
OA subjects were older than the RAs (M = 65.86, SD = 8.20, vs. M = 60.53, SD = 10.95), t(32) = 2.29, p < .05. They
also had slightly lower annual income (M = $35,000 vs. $27,500), t(33) = −2.57, p < .05, but subsequent analyses
showed that these income differences had nonsignificant effects on the measures under study. The illness characteristics
of the participants are provided in Table 1. The OA patients
showed less activity limitation and a lower weighted joint count
than did the RA patients. The clinician’s global assessment of
disease status did not differ between groups, and there were no
differences between groups in level of present pain reported
on a visual analogue scale. RAs tended to report slightly more
years with diagnosis than OAs, but the difference was not
statistically significant.

Table 2 contains analyses of differences between groups on
the major variables of interest in this study: life events, mental
health measures, and endocrine parameters. Endocrine values
were log transformed to reduce the skewness of their distribu-
tions. RAs differed from OAs in only one area: RAs reported
0.4 fewer symptoms of ill health unrelated to their arthritis
than did OAs. The similarity on these measures indicates that
the two groups are highly compatible in terms of life stress and
psychological distress and that they demonstrate no clear
disparity in mean levels of PRL, cortisol, and estradiol.

Patients were asked to identify all prescription and nonpre-
scription medications that they were taking from a 62-item
checklist. This list was corroborated by medical chart review.
From these data, we determined that 6 RA patients were
taking low dosages of methotrexate (a disease-modifying
drug), 14 were taking nonsteroidal anti-inflammatory drugs
(NSAIDs) only, and 6 were taking a combination of NSAID
therapy and methotrexate. Thirty-four of the OA patients were
taking NSAIDs. Additionally, 1 RA patient was on gold, 5
were on low-dose steroidal compounds, 2 were on antidepres-
sive medications, and 11 were taking over-the-counter anti-
inflammatory medications such as aspirin. Nine RAs and 14
OAs were on estrogen-replacement therapy.

Before assessing the relationships between stress and dis-
tress, we examined whether use of certain medications was
associated with scores on interpersonal stress, coping ineffi-
cy, depression, and the endocrine measures: cortisol, PRL,
and estradiol. Medications were grouped into seven types for analysis: antidepressive medications, low-dose steroids, nonsteroidal anti-inflammatory medications, disease-modifying medications, ulcer medications, pain medications, and estrogen. Pearson product–moment correlations were computed, and one- or two-tailed tests \( (p < .10) \) were used, depending on whether the direction of the relationship could be presumed on the basis of pharmacological effects of the drugs. Patients on estrogen replacement had higher scores on estradiol, \( r(60) = .39, p < .01 \), but showed no significant differences on other measures in the study at \( p < .10 \). Patients on low-dose steroid medications had lower scores on cortisol, as expected, \( r(60) = -.36, p < .01 \), but that medication was uncorrelated with any other measure. Patients on antidepressive medications reported more depression, \( r(60) = .27, p < .05 \); that relationship was most likely a consequence of the patient's depression leading the doctor to prescribe, rather than due to some paradoxical effects of the drug. Partial correlational analyses and partial regressions were performed to test whether controlling for the linear effects of low-dose steroids or estrogen replacement would affect the relationships among the variables; no significant effects were noted. The results are reported below, therefore, without controlling for these variables.

**Effects of Life Events and Coping Efficacy**

The correlations between depression and scores on interpersonal events, health problem events (not related to arthritis), and reports of coping inefficacy for RAs and OAs are shown in Table 3. As predicted, interpersonal conflict events were associated with higher scores on depression for both groups, and the effect was greatest in the RA sample. Noninterpersonal negative events were unrelated to depression for both groups. \( r(37) = .18, p > .10, \) for OAs; \( r(33) = .11, p > .10, \) for RAs. Positive interpersonal events and inefficacy in coping with stressful events other than arthritis had significant associations with depression in both groups. Health stressors not related to arthritis were correlated with depression for both groups, but not for OAs.

To examine further the apparent difference between RA and OA groups in the size of the correlations, multiple

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### Table 2

**Sample Characteristics: Life Events, Mental Health, and Endocrine Parameters**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rheumatoid arthritis</th>
<th>Osteoarthritis</th>
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<tbody>
<tr>
<td></td>
<td>( n )</td>
<td>( M )</td>
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<tr>
<td>Event measures</td>
<td></td>
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</tr>
<tr>
<td>Total small undesirable events</td>
<td>33</td>
<td>4.242</td>
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<tr>
<td>Total positive events</td>
<td>33</td>
<td>18.818</td>
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<tr>
<td>Nonarthritis health symptoms</td>
<td>33</td>
<td>0.667</td>
</tr>
<tr>
<td>Interpersonal conflict events</td>
<td>33</td>
<td>1.879</td>
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<tr>
<td>Positive interpersonal events</td>
<td>33</td>
<td>11.333</td>
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<tr>
<td>Mental health measures</td>
<td></td>
<td></td>
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<tr>
<td>Depression</td>
<td>33</td>
<td>2.34</td>
</tr>
<tr>
<td>Coping inefficacy for non-arthritis-related event</td>
<td>30</td>
<td>2.22</td>
</tr>
<tr>
<td>Coping inefficacy for flare-up</td>
<td>33</td>
<td>2.08</td>
</tr>
<tr>
<td>Endocrine parameters</td>
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<tr>
<td>Cortisol</td>
<td>22</td>
<td>0.99</td>
</tr>
<tr>
<td>Prolactin</td>
<td>22</td>
<td>0.46</td>
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<tr>
<td>Estradiol</td>
<td>22</td>
<td>-1.16</td>
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*p < .05.

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### Table 3

**Correlations Between Depression and Interpersonal Events, Health Symptoms, and Coping Inefficacy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Depression in RA( s )</th>
<th>Depression in OA( s )</th>
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<tr>
<td></td>
<td>( n )</td>
<td>( r )</td>
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<tr>
<td>Interpersonal events</td>
<td></td>
<td></td>
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<tr>
<td>Positive( a )</td>
<td>33</td>
<td>-.49**</td>
</tr>
<tr>
<td>Conflictual( b )</td>
<td>33</td>
<td>.68***</td>
</tr>
<tr>
<td>Nonarthritis health symptoms</td>
<td>33</td>
<td>.31*</td>
</tr>
<tr>
<td>Coping inefficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flare-ups</td>
<td>32</td>
<td>.28</td>
</tr>
<tr>
<td>Other events</td>
<td>32</td>
<td>.33*</td>
</tr>
</tbody>
</table>

*Note.* RAs = subjects with rheumatoid arthritis, OAs = subjects with osteoarthritis.

\( a \)Partial correlations, controlling for interpersonal conflict events.  \( b \)Partial correlations, controlling for positive interpersonal events.

\( *p < .05.  **p < .01.  ***p < .001.\)
regression analyses were performed with depression scores as the criterion. Predictors included centered scores on interpersonal events, scores on coping inefficacy during flare-ups, a dummy variable to classify subjects according to illness group (RA vs. OA), and product terms representing the interactions between interpersonal stress events and illness group and positive interpersonal events and illness group. Coping inefficacy with flare-ups was used in the equation, instead of coping inefficacy with other events, because it constituted a useful additional control over differences in depression resulting from differences in coping with illness-related stresses that were confounded with interpersonal stressors. In addition, group differences in age, activity limitation, and non-arthritis-related health events were controlled statistically by forcing them into the regression equation first, before assessing the effects of interpersonal events and their interactions with group status. The results are shown in Table 4.

There was a significant interaction effect in the prediction of depression. RAs showed higher elevations of depression than OAs when experiencing interpersonal conflict events. Positive interpersonal events and coping efficacy for arthritis-related events were associated with less depression in both OAs and RAs. There were no significant interactions between positive events or coping efficacy and illness group in the prediction of depression.

Effects of Stress and Depression on Endocrine Levels

If stress and poor coping efficacy are linked to disease activity, their effects might be mediated by increases in circulating levels of hormones that amplify the immune response, such as PRL and estradiol. Log-transformed scores on PRL and estradiol were summed to create a composite index of serum levels of immunostimulatory hormones. These scores were then correlated with measures of interpersonal conflict events, positive interpersonal events, depression, and coping inefficacy. In addition, multiple regression analyses were performed, to estimate the overall effect of psychosocial variables on stimulatory hormones for RAs and OAs, separately. The results of these analyses are shown in Table 5.

As would be expected from a model in which the effects of stress are mediated through changes in endocrine levels, higher interpersonal conflict was associated with higher levels of immunostimulatory hormones for RAs, and the positive relationship between depression and these hormones appeared to be even greater. Coping inefficacy was positively related to levels of immune-stimulating hormones and also to depression. In summary, those RA patients with higher scores on depression, and those who felt they coped poorly with stressful events, showed higher levels of stimulatory hormones. The findings were comparable when analyzing correlates of

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Note. N = 68. HAQ = Health Assessment Questionnaire, OA = osteoarthritis, RA = rheumatoid arthritis.
*p < .05. **p < .01.

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<td><strong>Correlations Between Stimulatory Hormones (Prolactin + Estradiol) and Psychosocial Factors and Clinician Ratings of Disease</strong></td>
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For subjects with rheumatoid arthritis, n = 22. For subjects with osteoarthritis, n = 28.
*p < .05. **p < .01.
Hormones Levels and Disease Status

were significant in the RA sample and approached significance with levels of immune-stimulating hormones. These effects global assessment of disease state were associated positively. 

was significant, $z$-difference score = 2.405, $p < .025$. Table 5 shows, both physician's joint count and physician's levels were correlated with assessments of disease status. As in the OAs. Cortisol levels in OA patients were uncorrelated between any single variable and group status (RA vs. OA) also. An $t(46)$, $p < .05$. Similar effects were not observed for OA patients; neither depression nor coping efficacy was related to stimulatory hormone levels for PRL and estradiol. Tests of differences in the size of correlations were nonsignificant. Interaction effects between any single variable and group status (RA vs. OA) also proved to be nonsignificant, although differences between OAs and RAs approached significance for coping inefficacy with flares in the expected direction, $t(46) = 1.76$, $p < .09$. An analysis of differences in overall effects due to the composites of psychosocial influences was conducted by comparing multiple $Rs$ obtained from the multiple correlational results (Tabachnick & Fidell, 1989). The overall difference in multiple $Rs$ was significant, $z$-difference score = 2.405, $p < .025$.

Correlational analyses were also performed for log transformed scores on cortisol. These findings were more ambiguous. For OA subjects, cortisol scores were not correlated with any of the psychosocial measures. For RA patients, neither coping inefficacy nor stressful events were significantly correlated with elevations in cortisol. Depression, however, was related to cortisol, $r(22) = .37$, $p < .05$.

**Hormones Levels and Disease Status**

To complete the test of our mediational model, hormone levels were correlated with assessments of disease status. As Table 5 shows, both physician's joint count and physician's global assessment of disease state were associated positively with levels of immune-stimulating hormones. These effects were significant in the RA sample and approached significance in the OAs. Cortisol levels in OA patients were uncorrelated with clinical ratings of disease activity ($ps > .10$). In RA patients, however, cortisol was correlated with higher (and not lower) clinician ratings of disease activity, $r(22) = .48$, $p < .05$, and was marginally correlated with joint count, $r(22) = .33$, $p < .15$.

**Path Model**

RA patients with greater interpersonal conflict showed a propensity toward greater depression, which in turn was associated with elevations in PRL, estradiol, and cortisol. These hormone elevations were in turn associated with evidence of greater disease activity. To examine this mediational model more formally, we conducted a path analysis, using the covariance matrices of relationships among scores on four variables for each group: interpersonal conflict events, depression, immune-stimulating hormones, and the clinician's global rating of disease activity. We limited the number of variables input to this analysis because of the small sample sizes involved. Coping inefficacy was left out of this analysis, even though it is an important variable, because that variable overlapped with depression in their relationship to hormone levels. A fully mediated effects model was tested for fit to the data for each group, with the size of the parameters relating the constructs free to vary among the groups. The results are shown in Figure 1.

The model fit the data well for the RAs, as evidenced by the nonsignificant chi-square statistic, a Tucker–Lewis goodness-of-fit index of .842, and significant path coefficients. The mediated model fit less well for the OA group, with a marginally significant chi-square and a poor Tucker–Lewis index. The small size of each sample precluded a direct statistical test of differences between models. Nevertheless, an important difference between the two groups was that all of
the parameters were statistically significant for the RA group, supporting a fully mediated model for the effects on interpersonal conflict events, but none of the parameters were significant for the OAs.

Discussion

The purpose of this investigation was to explore differences between RA and OA patients while testing the influences of psychosocial stressors on depression, hormone levels, and disease manifestations. The findings suggest that these two populations of arthritis patients do not differ in levels of stress and distress associated with their illness but may differ in the importance of stress and coping to psychological adjustment and also to physical health.

The two groups were quite similar on levels of pain, life stress events, positive events, and global assessments of the severity of their arthritis. They also showed no differences in level of depression or in their assessments of their efficacy in coping with arthritis and other stressful events. Furthermore, there were no significant differences in levels of PRL, cortisol, or estradiol between OAs and RAs. The overall similarity may be attributable to sampling frame, because all subjects were recruited from the waiting room of a large rheumatology practice and therefore all were likely to be symptomatic. For this study, the lack of group differences on these major variables was advantageous. It allowed us to compare the two groups’ psychological and endocrine responses to psychosocial stress.

The differences between groups that were obtained were expected. OAs were older, showed less overall disability, and had fewer joints involved in their disease than did RAs. These findings are consistent with medical facts about the illnesses: RA onset is earlier in life and is systemic, often attacking a number of joints bilaterally, in contrast to OA. The greater disability in RAs found in this study may be directly attributable to multiple joint involvement and the progressive nature of RA.

The relationship between interpersonal events and depression was substantial in both groups, but the proportion of variance accounted for was particularly dramatic in the RAs. Thus, although the mean levels of interpersonal conflict and depression did not differ in RAs and OAs, the relationship between them did. In keeping with prior studies by Jamison and Virts (1990), Manne and Zautra (1989), and Revenson and Felton (1984), those with stressful social interactions in the past month displayed greater depression, and independently, those with positive social events were less likely to show depressive symptoms. Individual differences in the frequency of other stressful events appeared to have little or no effect on depression, in comparison with the effects observed for interpersonal events. These results underscore the importance of the interpersonal arena among RA patients. They further suggest that future studies may benefit from the inclusion of a comprehensive inventory of interpersonal events such as was used here and possibly excluding the bulk of events dealing with noninterpersonal changes, to reduce the measurement burden on participants.

Why should RAs display greater reactivity to stressful interpersonal events than their counterparts in the OA population? We suspect that degree of attachment to the support system and expectancy of future dependence, both unmeasured in this study, may contribute to the differences obtained for negative interpersonal events. Because RA is a progressive disorder, the RA patient expects a decline in independent functioning, and this may heighten concern for a stable and supportive relationship, beyond that likely for the OA group. Parenthetically, it is not surprising that positive events did not vary in their effects between groups. Heightened sensitivity, if it is present, would most likely occur in response to those events that threaten to disrupt the social equilibrium, and not events that would enrich and enhance feelings of well-being.

Although the data are correlative, they also support the idea that RAs are more physiologically sensitive to psychosocial stress than are OA patients. RA patients showed positive relationships between the immunostimulatory hormones and depression, interpersonal conflict events, and coping inefficacy, whereas OA patients did not. These larger responses in RAs may be due to disease-related endocrine disregulation, or they may be related to the increased psychological responsivity already noted. Further study is needed to examine these possibilities. We hasten to add, however, that a distinction between psychological vulnerability and physiological sensitivity may be artificial; both body and mind may be more reactive to stress and emotional upset in the RA patient in comparison with controls.

The path analyses support a mediational model of the effects of interpersonal stress on the health of the RA patient. Note that the good fit of the mediational model does not mean that another model would not fit the data equally well. Indeed, it is possible that a reverse causal ordering of the variables would not lead to a large decrement in the goodness of fit of the data to the model. Nevertheless, the model fits our understanding of the nature of the disease, and how patients may become affected by the psychosocial sequelae of this chronic illness. Over the course of RA, flare-ups of the disease inevitably lead to joint damage and greater disability, and hence to greater dependence on caregivers. Thus, the pressure to cope with interpersonal demands is likely to be particularly troublesome for the RA patients, leading to increased depression and a reduced sense of efficacy. These factors, contributing possibly to an underlying cognitive schema of helplessness (Smith & Wallston, 1992), would then lead to a chronically stressful internal state, which would elevate PRL and estradiol levels. These hormones are known for their stimulatory effect on immune cells. They may in turn activate key immune mechanisms associated with greater inflammatory response, leading to a disease flare.

The findings presented here are not definitive. Indeed, this initial study may be viewed as one that poses hypotheses rather than testing them. The cross-sectional nature of the study limits the confidence we can have in the direction of the relationships implied in the path models and in the regression analyses. Furthermore, all possible effects of differences between groups in age and medications could not be examined; complex interactions may take place between endogenous hormones and the physiology of the patient with autoimmune disease that leads to changes in hormonal reactivity in ways not
yet understood. As our subjects were patients in an ongoing clinical practice, it was neither feasible nor ethical to manipulate their treatment, to estimate the total effects of medications.

This study also did not examine those immune system parameters that might forge a link between elevations in immune-stimulating hormones and joint inflammation. Indeed, we cannot be certain that the hormones we expected to be immune stimulating actually affected the immune parameters in the way we assumed. Estradiol, for example, although generally regarded as stimulatory of autoimmunity (Nelson & Steinberg, 1987), has been regarded by some as potentially inhibitory of some immune functions (e.g., Homo-Delarche et al., 1991) and may have different effects on RA patients than anticipated. Likewise, cortisol, long regarded as immunosuppressant, may not have its expected effect on patients with RA. The longitudinal assessment of change over time in the parameters under study here, with the addition of immune markers likely to covary with illness worsening such as interleukin-2 receptor scores (Harrington et al., 1993), would appear to be the next logical step in future research.

Even with its limitations, this study represents an important advance in research on this topic. For the first time, mediational linkages were established from a variable outside the body (stressful event measurement) through changes in internal messengers (immune-stimulating hormone levels) to disease state (clinician ratings of disease activity). Past studies have been able to establish correlations between exogenous variables and biological states such as hormonal levels or immune parameters or have identified relations between biological markers of disease activity and clinical levels of disease. To our knowledge, this is the first study of RA that has simultaneously demonstrated significant relationships at both links in this chain.

References


