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13. ABSTRACT *(Maximum 200 Words)* In addition to being a threat to physical health, breast cancer also represents a severe threat to psychological adjustment. Patients must confront a series of stressful experiences, including abnormal mammography results, biopsy/diagnosis, surgery, and chemotherapy. Our research examined the patterns and predictors of emotional distress in patients who chose to undergo adjuvant chemotherapy treatment and explored the possibility that distress might further increase the risk of infectious disease in these women whose immune defenses are already compromised by cytotoxic chemotherapy. Our studies indicate that patients' levels of distress are higher on treatment days than during the interval between chemotherapy infusions, and levels are particularly high prior to the first chemotherapy infusion. We have also found that the frequency of common infectious diseases (e.g., cold, flu) is higher among chemotherapy patients than among healthy age-matched comparison subjects, or patients' own level prior to chemotherapy. In addition, multilevel modeling analyses revealed that distress on infusion days predicted the frequency of infectious diseases during treatment. These results suggest that interventions to reduce distress might not only improve the quality of life, but might also reduce the risk of infectious disease in chemotherapy patients.

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INTRODUCTION

In addition to being a threat to physical health, breast cancer also represents a severe threat to psychological adjustment, which itself may be a threat to health . Patients must confront a series of stressful experiences, including abnormal mammography results, biopsy/diagnosis, surgery, and chemotherapy. Our research examined the patterns and predictors of emotional distress in patients who chose to undergo adjuvant chemotherapy treatment and explored the possibility that distress might further increase the risk of infectious disease in these women whose immune defenses are already compromised by cytotoxic chemotherapy.

BODY

Preliminary evaluation and modification of study procedures and measures.

In the first phase of the program of work, we reevaluated the feasibility of the proposed experimental design and methods of research, and made modifications necessary to adapt to aspects of clinical practice extant at our institution and to respond to patient/participant feedback concerning study burden. Several aspects of extant clinical practice were found to have implications for the study.

First, the move to an offsite clinic dedicated to chemotherapy for breast cancer and various associated changes in procedures reduced patient waiting time at their initial consultation regarding chemotherapy, as well as waiting time at treatment infusions. While a positive development for both patients and providers, the increased efficiency at initial evaluation visits, which were now conducted several blocks from our research offices, made it difficult to recruit participants at that time. We therefore modified our procedures such that participating oncologists provided a preliminary description of the study to their patients at that time and alerted the research nurse to contact interested patients at check in for their first scheduled chemotherapy infusion, at which time the study was described in more detail and written informed consent was obtained. Although this modification made recruitment of patient participants again feasible, it rendered the proposed Baseline Assessment (i.e., completion of the Life Experiences Survey, Interpersonal Support Evaluation Survey, and NEO-Five Factor Inventory) infeasible. Aspects of the proposed research involving those questionnaires were therefore dropped from study.

The enhanced efficiency at treatment clinic visits also reduced time available for participants to complete the proposed Clinic Assessment questionnaires (i.e., Profile of Mood States [POMS], and visual analogue scales [VASs]) particularly in the clinic prior to patients first infusion, because at that time, patients had to first complete written informed consent before completing any research materials. As time to explain the rationale and procedures for completion of the Daily Assessment Booklet was thus also extremely limited and there was sometimes resistance to the time commitment on the part of some potential participants, we did not make their agreement to complete the daily assessment a requirement for participation. Daily assessment data was therefore available on only a subset of the participants in the study and primarily served to confirm data collected at treatment infusions. In order to increase participation and reduce drop out, we also modified the daily assessment booklet to reduce the amount of time required for completion and allowed patients to decline phone call assessments from the research nurse if they found them unduly burdensome. Time pressure on clinical staff reduced the feasibility of using chart data to provide a reliable quantitative assessment of infectious signs and symptoms as proposed for the research. Therefore, greater reliance was placed on

a patient self-report questionnaire, which was administered in the clinic, to provide a quantitative retrospective assessment of patients' experiences of infectious disease (see Appendix). In order to reduce the time required for completion of the POMS in the clinic, we conducted a preliminary study of a short version of the POMS, as described in detail in the appended published manuscript (DiLorenzo et al., 1999). Because the short version of the POMS was found to have strong psychometric properties, with reliability and validity equivalent to the long version, we used it in place of the long version at all Clinic Assessments.

Second, as a result of changing clinical practice at our institution (and many others), it was no longer part of standard care for patients to asked to provide blood samples between treatment infusions for the assessment of chemotherapy-induced neutropenia (i.e, complete blood counts with differential [CBC]). In the absence of a clinical rationale and directive to provide any blood samples following chemotherapy infusions, we found patients' extremely resistant to the idea of providing repeated samples for research purposes, as originally proposed in the application. Insistence on the provision of the proposed schedule (every three days) of repeated blood samples as a condition of participation in the study would have yielded a minuscule patient sample that would likely have been unrepresentative of the whole, as a result of the sampling biases introduced and the possible effects of blood sampling on other measures (e.g., blood sampling might serve as a reminder of treatment and thus induce distress). We therefore dropped these assessments from the experimental design.

Emotional distress in adjuvant chemotherapy patients.

In the second phase of the program of research, we examined the patterns of emotional distress in a sample of 33 women who received a complete course of adjuvant systemic chemotherapy, as described in detail in the appended published manuscript (Montgomery et al., 1999), (see Appendix). Briefly, the results of this study indicated that breast cancer patients' emotional distress levels prior to their first infusion of chemotherapy were significantly higher than those of a healthy comparison group of women recruited from hospital staff. Interestingly however, patients' distress levels prior to subsequent chemotherapy infusions were relatively low across the course of repeated cycles of treatment and no longer differed from the levels seen in the healthy women staff members. Examination of available daily emotional distress data confirmed that distress levels showed a scallop pattern of increasing distress around the time of scheduled outpatient infusions of chemotherapy. The pattern of high levels of anticipatory distress prior to treatments, particularly the first, is consistent with an emerging view that these time windows are particularly stressful for many individuals confronting chemotherapy treatment. These data thus suggest the importance of investigating the potential negative impact of treatment related distress on patients' risks of infectious disease during treatment.

Effects of adjuvant chemotherapy on infectious disease levels.

In the third phase of the program of research, we sought to reconfirm the anticipated higher frequency of infectious disease among patients receiving adjuvant cytotoxic chemotherapy treatment for breast cancer. Our approach was to compare patients' frequency of infectious diseases after their first infusion of chemotherapy to: a) their own levels over the comparable interval immediately preceding chemotherapy (i.e., a within subject approach, comparing chemotherapy levels to prechemotherapy levels with each woman serving as her own control), b) to the frequency of infectious diseases reported by an age-matched group of healthy women (i.e., a between subject approach with healthy women serving as a comparison group) over comparable intervals. For this

study, we had 102 women in the Patient Group and 77 women in the Comparison Group with complete data required for the analyses. As shown in Table 1, levels of self-reported infectious diseases did not differ between the two groups before the patients began chemotherapy. Consistent with the study hypothesis however, after beginning chemotherapy, the patients had significantly higher levels of three types of infectious disease: common colds, gastrointestinal viruses, and mouth/lip sores, as well as a trend for an increased frequency of Flu. Interestingly, there was a significant main effect of group for vaginal infections, such that the patients had a higher frequency both before and after the start of chemotherapy. The absence of group differences on other types of infectious disease suggests that the significant differences that were found were not simply the result of a general bias to report disease on the part of patients. Thus, considered as a whole, the results support the view that chemotherapy increases the risk of infectious disease in breast cancer patients.

TABLE 1. Effects of Adjuvant Chemotherapy on Infectious Disease Levels

Reported Infectious Diseases	Study Group	Assessment 1 Mean[a] + SE	Assessment 2 Mean + SE
Cold	Chemotherapy Pts	0.22 ± 0.06	**0.73 ± 0.12***
	Healthy Comparison	0.35 ± 0.07	**0.39 ± 0.08***
Sinus Infection	Chemotherapy Pts	0.22 ± 0.08	0.25 ± 0.07
	Healthy Comparison	0.19 ± 0.08	0.16 ± 0.05
Flu	Chemotherapy Pts	0.04 ± 0.02	0.24 ± 0.07
	Healthy Comparison	0.06 ± 0.03	0.08 ± 0.04
GI virus	Chemotherapy Pts	0.08 ± 0.05	**0.31 ± 0.09***
	Healthy Comparison	0.08 ± 0.04	**0.06 ± 0.03***
Mouth/lip sores	Chemotherapy Pts	0.10 ± 0.03	**0.43 ± 0.09***
	Healthy Comparison	0.06 ± 0.03	**0.04 ± 0.02***
Urinary Infection	Chemotherapy Pts	0.02 ± 0.01	0.11 ± 0.05
	Healthy Comparison	0.00 ± 0.00	0.04 ± 0.02
Skin infection	Chemotherapy Pts	0.14 ± 0.05	0.23 ± 0.08
	Healthy Comparison	0.04 ± 0.03	0.10 ± 0.06
Vaginal infection	Chemotherapy Pts	0.12 ± 0.03	0.14 ± 0.06
	Healthy Comparison	0.04 + 0.02	0.05 ± 0.03

Note: Chemotherapy patient group N = 102; Healthy comparison group N
*Significant ($p \leq .05$) group difference
[a]Mean number of infectious episodes over the reporting window (e.g., 3 weeks)

Effects of emotional distress associated with chemotherapy on infectious disease levels.

In the fourth phase of the program of research, we examined the relationships between the levels of patients' emotional distress on days of treatment infusion and the levels of infectious diseases (frequency) over the interval following each of those infusions, using mutilevel linear model (MLM) statistical approaches. A *mixed linear model* is a generalization of the standard linear model, the generalization being that the data are permitted to exhibit correlation (as would be the case in repeated measures designs) and nonconstant variability (heterogeneous variances). MLM procedures, thus provide flexibility in modeling not only the means of the data (as in the standard linear model) but their variances and covariances as well. For present purposes, the MLM approach can be viewed as in effect allowing bivariate regressions (e.g., examining the relations between distress and infectious diseases in each chemotherapy cycle) to be analyzed in a repeated measures approach (across 7 cycles), covarying out prechemotherapy levels, without loss of subjects due to listwise deletion procedures for missing data. These analyses revealed significant relationships between patients' levels of emotional distress (total scores on the Profile of Mood States) and their levels (frequency) of the following infectious diseases: flu and mouth/lip sores, after controlling for baseline levels and other significant covariates (e.g., age). These results thus support the study hypothesis that chemotherapy patients with higher levels of emotional distress are at increased risk of at least some types of infectious disease.

KEY RESEARCH ACCOMPLISHMENTS

-Demonstrated that breast cancer patients' levels of emotional distress are higher prior to the first infusion of adjuvant chemotherapy than at any other infusion
-Demonstrated that patients' levels of distress are higher on treatment days than days between treatment infusions.
-Demonstrated that the levels of several infectious diseases in breast cancer patients are increased by chemotherapy treatment
-Demonstrated that the levels of some infectious diseases during chemotherapy are predicted by patients' levels of emotional distress at treatment infusions.

REPORTABLE OUTCOMES - See Appendix I.

CONCLUSIONS

Our studies have indicated that patients' levels of distress are higher on treatment days than during the interval between chemotherapy infusions, and levels are particularly high prior to the first chemotherapy infusion. We have also found that the frequency of common infectious diseases (e.g., colds, flu) is higher among chemotherapy patients than among healthy age-matched comparison subjects, or their own prechemotherapy levels of infection. In addition, multilevel modeling analyses revealed that distress on infusion days predicted the frequency of infectious diseases during treatment.

So what? These results suggest that interventions to reduce distress might not only improve the quality of life, but might also reduce the risk of infectious disease in chemotherapy patients

FINAL REPORTS:

Bibliography: See Appendix I

The following are employees that received some funding from Grant DAMD17-94-J-4141:

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APPENDIX I

REPORTABLE OUTCOMES

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REPORTABLE OUTCOMES

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Peer-Reviewed Publications

1. Montgomery GH, McClary KA, **Bovbjerg DH**. Adjuvant therapy for breast cancer and psychological distress. Annals of Oncology; 1996, 7: 977-979.

2. **Bovbjerg DH**. Commentary: Resistance, Psychoneuroimmunology, and the Common Cold. Mind/Body Medicine 1996; 1(4): 204-206.

3. DiLorenzo TA, **Bovbjerg DH**, Montgomery GH, Valdimarsdottir H, Jacobsen PB. The application of a shortened version of the profile of mood states in a sample of breast cancer chemotherapy patients. British Journal of Health Psychology 1999; 4: 315-325.

Non-Peer-Reviewed Publications

1. **Bovbjerg DH**, Stone AA. Stress and upper respiratory infection. In: Psychoneuroimmunology, Stress, and Infection, Friedman H, Klein T, Friedman AL (eds.), CRC Press: Boca Raton, FL, 1995; pp. 195-213.

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The U.S. Army Medical Research and Materiel Command, under DAMD17-94-J-4141 support this work.

Annals of Oncology 7: 977–979, 1996.

Letters to the editor

The Rosai–Dorfman Syndrome in a 17-year-old woman with transformation into high-grade lymphoma. A rare case presentation

The Rosai–Dorfman Syndrome, better known as sinus histiocytosis with massive lymphadenopathy (SHML), is a rare benign disease of unknown etiology. Persistent painless lymphadenopathy due to expansion of sinuses infiltrated with benign histiocytes and plasma cells is the characteristic feature of SHML [1]. Here, we present a rare case of Rosai–Dorfman Syndrome with transformation into high-grade lymphoma.

Case history

A 17-year-old white woman was admitted to the Cancer Center in Krakow. She had been referred by the local hospital where she was treated with antibiotics due to enlargement of cervical lymph nodes associated with fever. On admission, the patient presented massive cervical, bilateral lymphadenopathy, fever and general malaise. Chest X-ray and abdomen CT scan revealed no pathological changes. Eosinophilia was reported in the bone marrow aspirate. A cervical lymph node was excised and a histopathological diagnosis of Rosai–Dorfman Syndrome was established. An elevated erythrocyte sedimentation rate, leukocytosis, anemia and hypergammaglobulinemia were present. Flow cytometry revealed an immune dysfunction (decreased T-helper lymphocyte subpopulation). The result of an anti-HIV antibody test was negative. Cytogenetic studies were performed on bone marrow cells obtained from a sternal biopsy. All 35 analysed metaphases were normal, with karyotype 46, XX.

No treatment option was chosen. The patient was followed every 3 months and after 5 years of observation a rapid progression of the disease was documented. An excised axillary lymph node revealed a high-grade lymphoma. VACOP-B chemotherapy was administered and resulted in a clinical partial remission. Cervical lymph nodes and pharynx were treated with radiotherapy. A total dose of 5000 cGy in 25 fractions was given. The patient was in remission for 15 months.

The second-line chemotherapy with the ESA regimen was used due to recurrence. The patient has been in remission for 3 months with moderate doses of prednisone (15 mg) as maintenance therapy.

Discussion

The Rosai–Dorfman Syndrome is a very rare condition with a benign course. Spontaneous remissions have been observed, although severe immune dysfunction has been found to be associated with SHML [2]. In a literature review of 462 cases of this disease, the development of lymphomas was observed in 6 patients [3].

According to our observation and information from the literature [4], cases with transformation into non-Hodgkin's high-grade lymphoma require intensive treatment. It is possible that a complete remission cannot be achieved because of heterogenity of lymph node lesions (the co-existence of lymphoma and SHML cells) and observed remissions are associated with lymphoma component [5].

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Adjuvant therapy for breast cancer and psychological distress

Despite continuing improvements in the clinical management of aversive side-effects of chemotherapy treatment for cancer, there remains a widespread perception among health care professionals that patients experience increasing levels of emotional distress across the protracted course of infusions required for therapy [1, 2]. There is little empirical evidence to support this clinical impression, however.

We assessed emotional distress in 33 women receiving a complete course of adjuvant systemic chemotherapy, which consisted of a classic regimen of eight cycles of a standard combination of cytoxic agents, CMF (cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and 5-fluorouracil (600 mg/m^2)) i.v. q 21d. Eligibility criteria included: stage I or II breast cancer; post surgery (e.g., mastectomy); 18+ years old; not pregnant; received pretreatment chemotherapy teaching and uniform antiemetic treatments (i.v.), as part of routine clinical care. Few patients (mean = 1.8 patients per infusion) used anxiolytic or antiemetic medications (p.o.) prior to infusions. Emotional distress on the day of each treatment infusion was assessed with a short version of the

Profile of Mood States (POMS), a classic classic mood adjective checklist [3], which patients completed in the waiting room before each infusion. Healthy (self-report), female, hospital employees ($n = 31$) completed the POMS on a single occasion.

Patients' total distress scores (POMS) were highest prior to the first infusion of chemotherapy and then declined ($P < 0.01$) to levels comparable to distress scores of hospital employees (Figure 1). Only at Infusion-1 were patient distress levels significantly higher than employee levels ($P < 0.05$). Patients' distress levels were not predicted by: age, ethnic group, marital status, whether they were scheduled for another treatment modality (e.g., radiation), or by the number of positive nodes ($P > 0.05$), but were related to tumor size and cancer stage ($P < 0.05$). None of these factors affected the pattern of reduced distress following Infusion-1.

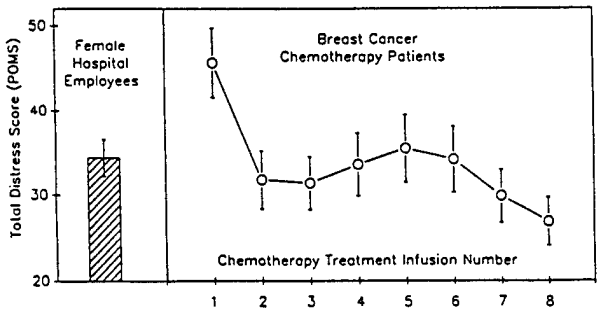

Figure 1. Changes in psychological distress scores (mean + SE) across a regimen of outpatient chemotherapy (CMF, i.v.) for breast cancer.

These results, based on patients receiving CMF, are consistent with our previous studies using single-item measures of distress [4, 5] and provide no support for the widespread view that patients typically develop more distress as they go through repeated cycles of chemotherapy treatment for cancer. To our knowledge all the available data indicate that patients' distress levels are higher prior to treatment than at any other time during chemotherapy. The sources of this pretreatment distress have yet to be determined, but may include negative expectations of side-effects, loss of control, and/or fear related to this novel experience.

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Rapid intravenous premedication with dexamethasone prevents hypersensitivity reactions to paclitaxel

Introduction

Paclitaxel is a highly active new drug in the treatment of various types of tumors; however, in early phase I testing [1], the speed of clinical development has been partially hampered by hypersensitivity reactions. In the subsequent clinical trials paclitaxel was administered by continuous infusion over 24 hours and a premedication regimen consisting of oral corticosteroids administered 12 and 6 hours before treatment, orphenadrine and cimetidine, was instituted; this premedication was successful in reducing the incidence of severe hypersensitivity reactions to less than 5% [2].

Moreover, the 3-hour infusion has also proven safe, but the timing of premedication is still rather cumbersome for routine use in the outpatient setting [3].

In the current report we compare the use of a rapid intravenous premedication with dexamethasone with standard prolonged oral premedication in patients treated with paclitaxel given over 3 hours.

Patients and methods

Patients with advanced cancer who had progressed after standard chemotherapy were eligible for paclitaxel.

All patients had histologically confirmed diagnoses of cancer; other eligibility criteria included: age ≤ 70 years, an ECOG performance status ≤ 2, normal bone marrow, liver and renal functions.

Standard premedication consisted of oral prednisone 125 mg 12 and 6 hours prior to paclitaxel infusion.

The intravenous premedication was approved by the local ethical committee and the patients gave their informed consent before treatment. Intravenous premedication consisted of dexamethasone 20 mg administered by intravenous bolus immediately before the start of paclitaxel.

All of the patients were also premedicated with intramuscular orphenadrine 50 mg plus intravenous cimetidine 300 mg one hour before start of treatment The calculated dose of paclitaxel was diluted in 500 ml of saline and administered over 3 hours. Only glass containers and polyethylene-lined tubing were used for drug delivery. In-line filtration of the prepared solution during paclitaxel infusion using cellulose acetate filters of 0.22 μm pore size was performed.

During paclitaxel administration blood pressure, heart rate and respiratory frequency were recorded every 20 minutes.

Severe hypersensitivity reactions were graded, according to WHO [3], as reactions with one or more of the following: angioedema, hypotension (SBP < 80 mmHg), respiratory distress requiring bronchodilators or generalized urticaria.

If any of these symptoms occurred, paclitaxel infusion was stopped and treatment for anaphylaxis with additional corticosteroids, antihistamines and bronchodilators instituted.

If mild or moderate symptoms of hypersensitivity occurred, the infusion was temporarily discontinued and 250 ml of saline were administrated before paclitaxel was started again.

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The application of a shortened version of the profile of mood states in a sample of breast cancer chemotherapy patients

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Objectives. The Profile of Mood States (POMS) is a 65-item mood measure with demonstrated reliability and validity; however, its length can be of concern to researchers. The present study investigated the utility of a 37-item shortened version of the POMS (SV-POMS) developed by Shacham (1983).

Design. In samples of breast cancer chemotherapy patients (patient group 1) and healthy volunteers, correlations between the subscales of the measures and internal consistencies were examined; these samples were also used to compare mood ratings of healthy women and patients. In another sample of breast cancer chemotherapy patients (patient group 2), the sensitivity to changes in mood of the measures was investigated.

Methods. Patient group 1 comprised 114 women; patient group 2 comprised 48 women. Healthy volunteers were 55 women recruited through newspaper advertisements.

Results. The correspondence between the measures was demonstrated by significant correlations of the shortened with the full-length scales. Internal consistencies of the measures were comparable. Both measures demonstrated mood differences between patients and volunteers. The responsiveness of the measures to change were comparable as demonstrated by changes in distress scores across chemotherapy infusions.

Conclusions. Results suggest that the SV-POMS can be used when participant burden is of concern.

Psychological well-being and distress are increasingly recognized as significant contributors to health, both for their role in quality of life and for their impact on susceptibility to physical illness (Cohen, Kessler & Gordon, 1996; Jekel, Elmore &

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Katz, 1996; Spilker, 1996). Assessment of emotional and affective functioning has thus taken on new importance in recent years (Naughton, Shumaker, Anderson & Czajkowski, 1996; Schipper, Clinch & Olweny, 1996; Stone, 1995). One of the most widely used instruments for the assessment of emotional states is the Profile of Mood States (POMS) (McNair, Lorr & Droppelman, 1971; Naughton *et al.*, 1996; Shumaker, Anderson & Czajkowski, 1990).

The POMS is a 65-item mood adjective checklist, which was developed by factor analysis to provide a self-report measure of six discrete mood states responsive to fluctuations in affect (McNair *et al.*, 1971). Respondents are asked to indicate how much each adjective applies to them on a 0 (not a all) to 4 (extremely) scale. Separate scores for each of the mood states are calculated by summing responses to each item in each of the six subscales. The subscales are as follows: tension–anxiety, depression–dejection, anger–hostility, fatigue–inertia, vigour–activity, and confusion–bewilderment. A Total Mood Disturbance score is calculated by summing the values of these six mood subscales, with vigour–activity items scored negatively. The POMS has been utilized with a wide range of populations, including cancer patients, psychiatric patients, and college students (McNair *et al.*, 1971; Cella, Tross, Orav, Holland, Silberfarb & Rafla, 1989; Shumaker *et al.*, 1990), and has been demonstrated to be sensitive to therapeutically induced change in clinical research (Goldberger & Brezinitz, 1982). Construct and predictive validity have been well established for the POMS and strong internal consistency has been demonstrated (McNair *et al.*, 1971).

As is the case for any self-report measure, clinically-orientated researchers are often concerned about the number of questions patients are asked to complete, particularly for participants who are not in good health (Shacham, 1983; Sutherland, Lockwood & Cunningham, 1989). In order to address this concern, shorter versions of the POMS have been published. An 11-item version developed by Cella and colleagues (Cella, Jacobsen, Orav, Holland, Silberfarb & Rafla, 1987) was designed to provide a Total Mood Disturbance score. While brief, this approach does not allow assessment of specific mood states, which many researchers may want to evaluate separately (e.g. fatigue; Bloom, 1990). Two shortened versions of the POMS which retain the subscale structure have also been reported. The first consists of six visual analogue scales (VAS), each selected to represent one mood dimension (Sutherland *et al.*, 1989). Correlations between subscales on this six-item VAS version with the corresponding full-length POMS subscales (assessed concurrently) were modest (range, $r = .61$ to .76) (Sutherland *et al.*, 1989). The second report has demonstrated stronger psychometric properties across subscales for a shortened POMS while eliminating 28 of the original 65 POMS items (Shacham, 1983).

In developing this shortened version, Shacham first administered the POMS (65 items) to 83 cancer patients with pain complaints. The contribution of each adjective to the internal consistency of its corresponding mood subscale was then examined. Items found to have higher internal consistency and judged to be face-valid were retained in this shortened version of the POMS (SV-POMS) (see Appendix). Examples of items that were excluded from the SV-POMS include 'shaky' from the tension–anxiety subscale, 'desperate' from the depression–dejection subscale, 'rebellious' from the anger–hostility subscale, 'carefree' from the vigour–activity subscale, 'sluggish' from the fatigue–inertia subscale, and 'muddled' from the confusion–bewilderment subscale. Shacham reported that scores on the six subscales and the Total Mood Disturbance scale of the SV-POMS

were highly correlated ($r = .95$ to .98) with the scores from the full-length POMS. Comparable levels of internal consistency were also found for the subscales and the Total Mood Disturbance scores (Shacham, 1983).

The purpose of the present study was to further investigate the utility of Shacham's SV-POMS in clinical research. First, using a group of healthy women (healthy participants) and a group of patients receiving adjuvant chemotherapy for breast cancer (patient group 1), we followed Shacham's methodology (Shacham, 1983) and examined the correlations between the SV-POMS and POMS scores within each of these groups. Second, within the same samples of participants, we investigated the internal consistency of the two scales by determining Cronbach's α values and item–total correlations. Third, we compared mood levels between patients and healthy volunteers on the SV-POMS and the full-length POMS to determine if the two versions would yield an identical pattern of results in a between-participants design. Finally, we explored changes in mood across chemotherapy infusions using the SV-POMS and full-length POMS in a second sample of patients (patient group 2) to determine if the two versions would yield an identical pattern of results in a within-participants design.

Method

Participants

Data for the present study were drawn from an ongoing programme of research assessing the biobehavioural effects of standard outpatient chemotherapy treatment for breast cancer. A consecutive series of women scheduled to receive intravenous adjuvant chemotherapy for breast cancer at a tertiary care cancer centre who met the following selection criteria were included: (1) diagnosed with Stage I or II breast cancer, status post radical, modified radical, or segmental mastectomy; (2) Karnofsky performance status over 70; (3) 18 years of age or older; (4) no neurological or psychiatric disorders; (5) English speaking; (6) satisfactorily completed the POMS (no missing data, as required for the analyses reported below). It should be noted that missing data in those few participants who were excluded from the study for failure to rate each POMS mood adjective (2.8%) were scattered across the form suggesting momentary lapses of attention rather than a systematic pattern of omissions. All patients received standard combinations of the following chemotherapy agents: cyclophosphamide; methotrexate; 5-fluorouracil; and/or adriamycin on a 3-week cycle (i.e. an infusion once every 21 days).

Patient group 1 consisted of 114 women receiving chemotherapy for breast cancer. Women in this group completed the POMS early in the course of chemotherapy treatment. Patients ranged in age from 28 to 74 years ($M = 48$, SD = 11.5 years). This sample was predominately white (70%), married (66%), and well-educated, with 59% having at least a college degree. Most patients were working at the start of chemotherapy (54%).

Patient group 2 included 48 women receiving chemotherapy for breast cancer. Women in this group completed the POMS immediately before their first two infusions of chemotherapy. These women ranged in age from 29 to 71 years ($M = 48.1$, SD = 9.95 years). Again, the majority of patients were white (83%), married (64%), and employed (56%), and 45% had college degrees.

Healthy participants were recruited through advertisements in local newspapers as part of the ongoing programme of research on the effects of chemotherapy. Participants who reported no current chronic or acute illnesses, no history of cancer, and were available to be scheduled for assessment at the same time as a cancer patient, were included in the present study. These 55 women ranged in age from 22 to 80 years ($M = 37$).

The sample was predominately white (75%), single (56%) and well-educated, with 85% having at least a college degree. Most were employed (83%) at the time of assessment.

Measures

Profile of Mood States. The POMS (McNair *et al.*, 1971) is a 65-item adjective checklist which asks respondents to rate how they have been feeling on a 5-point scale (ranging from 'not at all' to 'extremely') for each mood adjective. Subscale scores are calculated by summing the items comprising each particular participants subscale. Seven items are included as 'filler' and are not scored. The Total Mood Disturbance score is calculated by summing the results of the six mood subscales, with the items on the vigour–activity subscale weighted negatively.

SV-POMS. The SV-POMS (Shacham, 1983) is a shortened version of the POMS that consists of the 37 items from the POMS that were found to have higher internal consistency and judged to be face-valid in a study of cancer patients. The SV-POMS retains the six mood subscales from the POMS. Subscale scores are calculated by summing the items comprising each particular subscale and dividing by the number of items in the subscale.

Procedures

Following the procedures of Shacham (1983), the SV-POMS and the 65-item POMS (McNair *et al.*, 1971) were administered to all participants at the same time. Instructions directed participants to rate how they have been feeling 'today.' As part of the ongoing research from which this sample was taken, the POMS was individually administered by a trained research interviewer to participants in patient group 1 at home after their second chemotherapy infusion. The POMS was individually administered to the healthy participants by a trained research interviewer in a research office at the medical centre. The POMS was individually administered to patient group 2 participants by a trained research interviewer in the clinic waiting area, immediately prior to their first and second chemotherapy infusions, which occurred 3 weeks apart.

Statistical analyses. Data from patient group 1 and the healthy participants were used to generate Pearson's correlation coefficients. The correlations between subscale and Total Mood Disturbance scores on the SV-POMS and full-length POMS were calculated to examine the correspondence between the two versions of the POMS.

Cronbach's α coefficients and item–total correlations were computed for patient group 1 and the healthy participants to examine whether the SV-POMS subscales and Total Mood Disturbance scale possessed levels of internal consistency similar to their full-length counterparts.

Data from patient group 2 were entered into repeated measures analysis of variance designs to compare the responsiveness of the two versions of the POMS to changes in mood known to occur between patients' first and second chemotherapy infusions (Jacobsen, Bovbjerg & Redd, 1993; DiLorenzo, Jacobsen, Bovbjerg, Cheng, Hudis & Sklarin, 1995; Montgomery, McClary & Bovbjerg, 1996). All analyses were performed using SAS statistical software (SAS Institute, 1988).

Results

Correlations between scores on the SV-POMS and scores on the POMS in two independent samples of participants

As shown in Table 1, individual subscale scores and Total Mood Disturbance scores of the SV-POMS were all highly correlated with the corresponding scales of the full-length POMS (range, $r = .93$ to .99) in the two independent samples of participants, patient group 1 and the healthy participants.

Table 1. Comparison of the full-length Profile of Mood States (POMS) and the Shortened Version of the Profile of Mood States (SV-POMS) in two independent samples of participants

Scale	Number of items		Correlations between scores[a]	
	POMS	SV-POMS	Healthy participants r	Patient group 1 r
Tension–anxiety	9	6	.99	.97
Depression–dejection	15	8	.98	.96
Anger–hostility	12	7	.97	.94
Vigour–activity	8	6	.99	.98
Fatigue–inertia	7	5	.99	.99
Confusion–bewilderment	7	5	.96	.93
Total Mood Disturbance	58[b]	37	.99	.98

[a]Pearson's correlations between scores on the full-length POMS and scores on the SV-POMS in each of the two independent groups of participants: $p \leq .0001$.
[b]Seven items in the POMS are included as filler items and are not included in subscale or total mood-disturbance scores.

Psychometric properties of the SV-POMS and the POMS in two independent samples of participants

To assess the internal consistency of the measures, Cronbach's α coefficients, which estimate whether items in a given scale are cohesive and measure the same psychological construct, were computed. Internal consistencies of the SV-POMS subscales were similar to those of the full-length POMS in both patient group 1 and the healthy participants (Table 2). Cronbach's α values for the SV-POMS subscales ranged from .62 to .93 in patient group 1 and from .73 to .97 in the healthy participants; the range for the full-length subscales was .58 to .93 for patients and .80 to .96 for healthy volunteers. It should be noted that the lower α values for the confusion–bewilderment subscale found here are consistent with previous reports in the literature (e.g. McNair *et al.*, 1971).

Table 2. Psychometric properties (Cronbach's α coefficients) of the full-length Profile of Mood States (POMS) and the Shortened Version of the Profile of Mood States (SV-POMS) in two independent samples of participants

Scale	Healthy participants		Patient group 1	
	POMS α	SV-POMS α	POMS α	SV-POMS α
Tension–anxiety	.91	.90	.84	.86
Depression–dejection	.96	.95	.89	.87
Anger–hostility	.96	.97	.87	.90
Vigour–activity	.95	.95	.91	.93
Fatigue–inertia	.94	.94	.93	.92
Confusion–bewilderment	.80	.73	.58	.62
Total Mood Disturbance	.97	.96	.94	.93

To examine further the internal consistency of the measures, the correlations of individual items with the sum of the remaining items on a particular subscale were calculated for both the SV-POMS and POMS in patient group 1 and the healthy participants. The range, mean, and standard deviation of these item–total correlations for each subscale are presented in Table 3. With the exception of confusion–bewilderment, mean correlations for the SV-POMS subscales were equal to or higher than those of the corresponding POMS subscales in both samples.

Table 3. Psychometric properties (item-total correlations) of the full-length Profile of Mood States (POMS) and the Shortened Version of the Profile of Mood States (SV-POMS) in two independent samples of participants

	Healthy participants						Patient group 1					
	POMS			SV-POMS			POMS			SV-POMS		
Scale	Mean	(SD)	Range	Mean	(SD)	Range	Mean	(SD)	Range	Mean	(SD)	Range
Tension–anxiety	.74	(.12)	.54–.90	.78	(.11)	.61–.90	.63	(.15)	.32–.80	.73	(.06)	.64–.69
Depression–dejection	.79	(.10)	.57–.88	.84	(.04)	.77–.89	.70	(.09)	.54–.81	.72	(.10)	.50–.80
Anger–hostility	.79	(.10)	.58–.90	.85	(.06)	.77–.91	.64	(.17)	.27–.83	.75	(.07)	.62–.82
Vigour–activity	.80	(.07)	.63–.88	.82	(.06)	.70–.88	.67	(.09)	.52–.78	.71	(.06)	.59–.80
Fatigue–inertia	.71	(.08)	.58–.80	.71	(.08)	.59–.82	.79	(.09)	.59–.86	.82	(.04)	.75–.86
Confusion–bewilderment	.58	(.13)	.35–.73	.56	(.10)	.51–.67	.52	(.12)	.35–.69	.50	(.08)	.40–.59
Total Mood Disturbance	.65	(.14)	.38–.88	.67	(.14)	.38–.88	.58	(.13)	.21–.77	.61	(.10)	.29–.79

Detection of differences between participant groups using the SV-POMS and the POMS

Differences in mood between cancer patients and healthy volunteers have been documented previously (Nerenz, Leventhal & Love, 1982). To confirm the utility of the SV-POMS in detecting such differences, we compared a group of patients to a group of healthy volunteers with regard to their Total Mood Disturbance and subscale scores using both the SV-POMS and the full-length POMS (see Table 4). As expected, analyses of variance confirmed that the cancer patients (patient group 1) had higher Total Mood Disturbance scores on the POMS than the healthy participants. The SV-POMS also revealed a significant group difference in Total Mood Disturbance scores. Both the POMS and the SV-POMS revealed significant group differences on the following subscales: tension–anxiety, depression–dejection, anger–hostility, fatigue–inertia and confusion–bewilderment. Neither version revealed differences for vigour–activity. Thus, the between-participants analyses of the SV-POMS revealed an identical pattern of group differences as the full-length POMS.

Responsiveness to changes in mood scores using the SV-POMS and the POMS

Distress levels have been shown to be particularly high in cancer patients awaiting their first infusion of chemotherapy; once patients have experienced chemotherapy and had their worst fears disconfirmed, this heightened distress is no longer evident (DiLorenzo *et al.*, 1995; Jacobsen *et al.*, 1993; Montgomery *et al.*, 1996). To confirm the utility of the SV-POMS in detecting the reduction in distress after patients have had experience with

Table 4. Statistical analyses (ANOVA) of the scores of the full-length Profile of Mood States (POMS) and the Shortened Version of the Profile of Mood States (SV-POMS) reveal an identical pattern of differences in mood states between healthy participants and cancer chemotherapy patients

	POMS[a]						SV-POMS					
	Healthy participants		Patient group 1		Statistics		Healthy participants		Patient group 1		Statistics	
Scale	Mean	(SD)	Mean	(SD)	F	$p \leq$	Mean	(SD)	Mean	(SD)	F	$p \leq$
Tension–anxiety	.37	(0.86)	.72	(0.79)	16.12	.01	.80	(0.97)	1.22	(0.95)	19.07	.01
Depression–dejection	.45	(0.77)	.57	(0.66)	4.03	.05	.50	(0.86)	.70	(0.77)	6.10	.02
Anger–hostility	.45	(0.81)	.59	(0.67)	4.96	.03	.52	(0.93)	.68	(0.83)	6.91	.01
Vigour–activity	−2.04	(1.06)	−1.97	(0.84)	0.00	.99	−2.08	(1.10)	−2.02	(0.90)	0.02	.88
Fatigue–inertia	.77	(0.79)	1.40	(1.04)	23.52	.01	.87	(0.85)	1.56	(1.11)	25.24	.01
Confusion–bewilderment	.14	(0.64)	.33	(0.62)	6.59	.02	.59	(0.66)	.85	(0.67)	11.21	.01
Total Mood Disturbance	.10	(0.67)	.32	(0.60)	10.02	.01	.20	(0.73)	.48	(0.67)	13.41	.01

Note. Hypothesis testing for mood differences between healthy participants and cancer patients with the critical value set at the conventional $p = .05$, yields identical results for the POMS and SV-POMS on every subscale.
[a]Scores for the SV-POMS and POMS were transformed by dividing each subscale score by the number of items on the subscale.

chemotherapy, we assessed mood in the clinic prior to the first and second chemotherapy infusions for a group of breast cancer patients (patient group 2). As anticipated (DiLorenzo *et al.*, 1995; Jacobsen *et al.*, 1993; Montgomery *et al.*, 1996), repeated measures analyses of variance revealed a significant decrease in Total Mood Disturbance scores from infusion one to infusion two on the full-length POMS. The SV-POMS also revealed a significant decrease in Total Mood Disturbance after the first infusion (see Table 5). Both versions of the POMS also revealed significant within-participant changes for tension–anxiety, depression–dejection, and confusion–bewilderment. Neither version revealed a significant change for fatigue–inertia or anger–hostility. The SV-POMS revealed a significant change in vigour–activity, whereas the POMS did not ($p < .09$). Thus, the SV-POMS revealed a similar pattern of changes in mood to the full-length POMS with the exception of the vigour–activity subscale, which yielded inconsistent results with repeated measures ANOVA.

Discussion

The results of the present study reconfirm and extend the findings reported by Shacham in his development of the 37-item SV-POMS (Shacham, 1983) with cancer pain patients. The present authors report for the first time the applicability of the SV-POMS to samples of healthy individuals as well as breast cancer chemotherapy patients. The SV-POMS demonstrated similar psychometric properties to the full-length POMS in these two independent samples of participants. This shorter version of the classic mood adjective checklist also demonstrated the capability to discriminate differences in mood between groups of people, and to be responsive to changes in mood within a group of people.

In the present study, scores on Total Mood Disturbance and individual subscales using the SV-POMS were found to be highly correlated with scores on the full-length POMS.

Table 5. Statistical analyses of the results of the full-length Profile of Mood States (POMS) and the Shortened Version of the Profile of Mood States (SV-POMS) reveal a similar pattern of changes in mood states between patients' first and second infusions of chemotherapy

	POMS						SV-POMS					
	Infusion 1		Infusion 2		Statistics		Infusion 1		Infusion 2		Statistics	
Scale	Mean	(SD)	Mean	(SD)	F	$p \leq$	Mean	(SD)	Mean	(SD)	F	$p \leq$
Tension–anxiety	1.66	(0.95)	.75	(0.67)	55.03	.01	1.43	(0.68)	.81	(0.46)	56.30	.01
Depression–dejection	.53	(0.57)	.32	(0.54)	7.12	.01	.49	(0.52)	.26	(0.42)	13.17	.01
Anger–hostility	.37	(0.47)	.27	(0.54)	1.25	.27	.34	(0.38)	.26	(0.44)	1.65	.20
Vigour–activity	−2.01	(0.92)	−2.56	(0.86)	2.92	.09	−2.00	(0.85)	−2.22	(0.76)	3.48	.02
Fatigue–inertia	.72	(0.83)	.78	(0.68)	0.19	.66	.64	(0.73)	.67	(0.62)	.07	.79
Confusion–bewilderment	.80	(0.77)	.46	(0.52)	15.68	.01	1.04	(0.53)	.78	(0.36)	16.91	.01
Total Mood Disturbance	.33	(0.52)	.05	(0.44)	16.12	.01	.35	(0.42)	.12	(0.34)	18.45	.01

Note. Hypothesis testing for mood changes between infusion 1 and infusion 2 with the critical value set at the conventional $p = .05$, yields identical results for POMS and SV-POMS on every subscale except one (vigour–activity).

In addition, the two versions of the POMS showed similar levels of internal consistency (α and item–total correlations) across subscales in both patient and healthy volunteer samples. It is noteworthy that the two versions were consistent in revealing lower levels of internal consistency for the confusion–bewilderment subscale, a limitation of this particular subscale that has been recognized since the development of the POMS, and argues against its use in isolation.

The SV-POMS was also similar to the full-length POMS in its sensitivity to detect both between-participant and within-participant differences in mood. Although the significant differences in mood between chemotherapy patients and healthy volunteers should be interpreted cautiously (because these samples were not matched on a number of demographic variables and the sample sizes were modest) the results confirmed that the SV-POMS reveals a similar pattern of differences in mood subscales between patients and healthy volunteers to that seen with the full-length POMS. Although these results suggest that the POMS and SV-POMS have comparable sensitivity for the detection of group differences in moods, it should be noted that one cannot compare the absolute values of the scores, because the items included in the SV-POMS were selected based on their face validity and high levels of internal consistency, rather than with the intention of yielding identical means. For that reason, one limitation of using the SV-POMS is that the mean values cannot be compared directly to published historical data for the full length POMS (e.g. norms). Providing further support for the sensitivity of the SV-POMS, the results presented here indicated that the SV-POMS was as responsive as the POMS to changes in mood known to occur in patients after they have experienced chemotherapy (DiLorenzo *et al.*, 1995; Jacobsen *et al.*, 1993; Montgomery *et al.*, 1996).

While reducing the number of items from 65 to 37, the SV-POMS retains several features of the POMS that have contributed to its popularity. One important feature of the POMS is that the six subscales can be administered individually. For example, several individual subscales of the full-length POMS including anxiety (Glaser, Kiecolt-Glaser, Bonneau, Melarkey, Kennedy & Hughes, 1992), fatigue (Bloom, 1990), and depressed mood (Malouff, Schutte & Ramerth, 1985) have been used separately to assess specific

mood states. The SV-POMS retains these six specific subscales in addition to providing a Total Mood Disturbance score. The option of separately administering individual SV-POMS subscales may be important for investigators whose interests are focused on one or more specific mood states.

The SV-POMS also appears to retain the temporal flexibility of the POMS, which enables investigators to modify the time window for which mood is being assessed. The POMS has been used to assess mood over several different time frames including 'right now,' 'today,' and 'the past week, including today' (McNair *et al.*, 1971; Shacham, 1983). In fact, in McNair and colleagues' original studies (McNair *et al.*, 1971), the factor structures of the full-length POMS were found to be identical when participants were directed to answer for 'right now' and for 'the past week, including today'. The temporal flexibility of the SV-POMS is suggested by the similar results found in the present study in which participants reported mood state for 'today,' and in Shacham's study (Shacham, 1983) in which mood was assessed for 'the past week, including today.' Such flexibility may be important for investigators who are interested in assessing the effects of time-limited events, such as behavioural interventions or medical procedures.

Another positive feature of the POMS is its generalizability across a wide range of participant populations (McNair *et al.*, 1971; Shacham, 1983). Consistent with the generalizability of the SV-POMS are the results of the present study, which included samples of both healthy women and breast cancer chemotherapy patients. It appears that the SV-POMS, like the full-length POMS, can be used with a variety of participant populations. The SV-POMS also retains several features of the POMS not retained in other published shortened versions. For example, the 11-item version developed by Cella and colleagues (Cella *et al.*, 1987) yields a Total Mood Disturbance score, but does not include any of the mood subscales. One other shortened version of the POMS that does retain the mood subscales consists of six VAS (one for each mood dimension) (Sutherland *et al.*, 1989). However, correlations between scores on the subscales of the full-length POMS and the VAS subscale scores were lower than the correlations found using subscale scores from the SV-POMS in the present study.

The results of the present study support the conclusion that the SV-POMS is a psychometrically sound measure of mood state that retains many important features of the POMS, while reducing participant burden by requiring completion of substantially fewer items. The reduction in participant burden may be especially important for investigators interested in measuring mood state in medical patients undergoing aversive diagnostic or treatment procedures. Use of shortened versions of classic questionnaires, such as the SV-POMS, will probably increase acceptability to participants who may be physically and/or emotionally compromised, thus increasing participation rates and the generalizability of study samples. The practical benefits to investigators of using the SV-POMS may include reduced time of administration, scoring and data entry.

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Appendix

Items included on the SV-POMS, listed by subscale

Tension–anxiety	*Depression–dejection*	*Anger–hostility*
Tense	Unhappy	Angry
On edge	Sad	Peeved
Uneasy	Blue	Grouchy
Restless	Hopeless	Annoyed
Nervous	Discouraged	Resentful
Anxious	Miserable	Bitter
	Helpless	Furious
	Worthless	

Vigour–activity	*Fatigue–inertia*	*Confusion–bewilderment*
Lively	Worn out	Confused
Active	Fatigued	Unable to concentrate
Energetic	Bushed	Bewildered
Cheerful	Exhausted	Forgetful
Full of pep	Weary	Uncertain about things
Vigorous		

Commentary: Resistance, Psychoneuroimmunology, and the Common Cold

When the Editors asked me to write a commentary on the article by Drs. Caudell, Gallucci, and Betrus scheduled for publication in the current issue of *Mind/Body Medicine*, I was intrigued by the title: "A Psychoneuroimmunologic Perspective of Resistance: Implications for Clinical Practice." I assumed that resistance to infectious disease, so clearly related to immune defenses, would be the central focus of the article. However, given the breadth of the "illnesses" (e.g., headaches to cancer) apparently encompassed by the authors' concept of resistance it is perhaps not surprising that the article has little room for detail regarding any particular type of illness.

Because one of my areas of research interest over the past several years has been psychoneuroimmunology and infectious disease, I would like to take the opportunity to provide some additional comments specifically addressed to psychosocial factors, immune function, and infectious disease in humans. This is not the place to provide an exhaustive review of the literature implicating psychosocial factors as moderators of infectious disease, or the even more voluminous literature devoted to investigation of immune defenses against infection in both humans and animals; such reviews have recently been published.[1-6] Rather, I propose to highlight some recent findings from human studies of upper respiratory illness, to comment on some of the conceptual and methodologic complexities involved in this area of research, and to emphasize the many critical research questions yet to be addressed. Although many of my comments are based upon a more thorough consideration of these topics in a chapter that I recently coauthored with Dr. Arthur Stone,[1] it should be noted that the opinions expressed below do not necessarily reflect those of Dr. Stone.

The studies on psychosocial factors and infection specifically cited by Drs. Caudell, Gallucci, and Betrus represent just the tip of a large and venerable "iceberg" of research on this topic. A number of recent reviews of this work are available. The book "Psychoneuroimmunology, Stress, and Infection" includes reviews of the elegant ongoing psychoneuroimmunologic research on infection in animals.[2] Review articles in journals, from researchers active in the area, include recent reports by Cohen and Williamson,[3] whose emphasis is on psychological factors in humans; Peterson and colleagues,[4] whose emphasis is on biologic factors in both humans and animal models; and Boyce and Jemerin,[5,6] whose emphasis is on children and individual difference variables, such as reactivity, that may contribute to their susceptibility to infectious disease.

This literature suggests that there are at least five steps in the pathogenesis of infectious disease where psychological and behavioral factors could influence the outcome: (1) the exposure to the pathogen, (2) the host mechanisms to prevent infection and to limit replication of the infectious agent, (3) the symptoms associated with the infection, (4) the mechanisms responsible for recovery from the infection, and (5) the generation of immunologic memory to protect against future infection.[1] The possible impact of psychological and behavioral variables on each of these five steps is discussed below, using the example of the common cold. This example was chosen for two reasons. First, familiar to all of us from personal experience, colds are among the most prevalent of infectious diseases in the United States.[7] Second, the most compelling evidence of the impact of psychological factors on infectious disease comes from recent studies of colds experimentally induced in human volunteers by nasal administration of live virus.

Step 1: Exposure to the virus. It has been recognized since the time of Pasteur that exposure to an infectious agent is the *sine qua non* of infectious disease. In the case of a common cold, the infectious agent is typically, but not exclusively, one of the more than 100 different types of rhinoviruses (serotypes) that have now been isolated.[7] Because the nasal secretions of an infected individual can contain extremely high concentrations of live virus, exposure to the virus often comes from airborne droplets and aerosols (e.g., from a sneeze) that reach the mucus membranes of the nose or eyes. Because the virus can live for several hours on common household objects, one can also contract the virus by touching the mucus membranes of the eyes or nose after touching something (e.g., a doorknob) previously contaminated by nasal secretions from an infected individual. As might be expected, children are a major source of environmental exposure to cold viruses; parents experience more colds than other adults.[8] These considerations suggest that exposure to cold viruses cannot be treated as a stochastic process in studies attempting to link psychological variables to infection. Psychological and behavioral variables may well have an impact on the likelihood of viral exposure. For example, one effective means that individuals may employ for coping with life stressors is to seek out social support.[9] However, increased levels of social interaction may increase the risk of exposure to a cold virus; for example, visiting a friend who happens to have a cold or have children with a cold. Other possibilities include psychological influences on aspects of personal hygiene (e.g., frequency of hand washing) known to affect transmission of cold viruses.[7] These potential influences of psychological variables on exposure to a cold virus highlight the difficulties of proving that alterations in immune defenses mediate any relations

found between psychological variables and infection in naturalistic studies.

Step 2: Host mechanisms to prevent infection and/or to limit viral replication. There are a number of nonspecific and specific defense mechanisms that can prevent viral attachment to the epithelial surface, thus reducing the likelihood that an infection will become established in individuals exposed to a cold virus. For example, ciliary movement of the outer layer of mucus serves to sweep particles toward the posterior pharynx, where they can be harmlessly swallowed.[10] Because behavioral factors, such as smoking, may adversely affect these nonspecific defenses, one must consider possible indirect effects of psychological variables (e.g., stress-induced increases in smoking) on infection.

A more specific mechanism that also serves to prevent viral attachment and prevent spread of the virus is provided by the presence in nasal secretions of antibodies (predominantly, but not exclusively, secretory immunoglobulin A [sIgA]) to specific rhinoviruses. It has been recognized for many years that individuals who have higher levels of specific antibodies for any given rhinovirus are less likely to subsequently become infected following exposure to that particular rhinovirus.[7] Because this inverse correlation between levels of specific sIgA and risk of infection is true whether the sIgA is measured in nasal secretions or in peripheral blood, some investigators argue that circulating antibody may be important for long-lasting immunity to particular viruses.[11] Cellular immune defenses, such as cytotoxic T-cell activity against cells infected with rhinovirus, also may play a role in preventing an infection from becoming established, but research is scant.[12] It is clear, however, that T cells play a major helper role in the synthesis of IgA by B cells.[13]

The potential impact of psychological factors on immunologic defense mechanisms is suggested by the accumulating evidence from the psychoneuroimmunology research on humans reviewed by Dr. Caudell and colleagues. It should be noted, however, that the vast majority of those studies involve nonspecific immune measures (e.g., mitogen responses) of lymphocytes isolated from peripheral blood. Whether such measures are predictive of the likelihood of rhinovirus infection has yet to be established. On the other hand, support for the possible influence of psychological factors on an immune measure with more obvious relevance to rhinovirus infection comes from a recent study of salivary IgA responses to repeated oral immunization with a novel protein antigen.[14] In this study, Stone and colleagues found a positive relation between specific IgA levels and daily measures of positive events and positive mood, as well as a negative relation of IgA levels with negative events and negative mood.[14] The mechanisms responsible for these relations remain to be determined. It is important to remember that, in addition to possible neuroendocrine mediation of relations between psychological variables and immune variables, changes in behaviors known to affect the immune system, such as sleep patterns, consumption of alcohol, etc., may also play a mediating role.

Step 3: Symptoms associated with infection. The symptoms of a common cold, for example, runny nose, sneezing, sore throat, are familiar to all of us, but it is not widely appreciated that these symptoms are not an inevitable consequence of a rhinovirus infection.[7] Experimental studies in which volunteers undergo nasal inoculation with live rhinovirus have indicated that about a third of all subjects who develop a viral infection, as documented by high levels of the rhinovirus in nasal secretions, do not experience any symptoms of a cold. These results are not an artifact of the experimental setting, because similar findings have been reported in field studies that directly assessed nasal rhinovirus levels.[7] Although the mechanisms responsible for the typical symptoms of a cold have yet to be fully elucidated, the critical role of host responses to the virus in the generation of symptoms has been well established.[1] Infection is thought to result in the release of local inflammatory mediators (e.g., kinins), which in turn cause the symptoms.[15] A possible role for immune defenses in the generation of symptoms is suggested by studies demonstrating a positive relation between the severity of symptoms and the number of lymphocytes and neutrophils found in nasal secretions.[16] Symptoms also may be due, in part, to virally induced activation of nerve fibers in the nasal mucosa that are thought to regulate the release of nasal secretions (including sIgA) from serous and mucous glands.[17]

This brief overview of research on the mechanisms responsible for the symptoms of the common cold has two important implications for studies of psychoneuroimmune mediation of relations between psychological factors and the common cold. First, the biological pathways that mediate putative psychological effects on infection may be different from those that mediate effects on the symptoms of the infection. Consistent with this possibility, there have now been three separate studies documenting relations between cold symptoms and psychological variables, independent of relations to infection per se.[18–20] Moreover, there is some indication of selective effects, such that certain psychological variables, such as negative affect, may be more related to infection, whereas other variables, such as life events, may be more related to symptomatology within infected individuals.[18–20] Second, the likely involvement of local neural influences over nasal secretory processes in the symptoms of a cold raises the possibility that some psychological influences on symptoms will prove to be independent of psychological effects on the immune system.

Step 4: Mechanisms responsible for recovery from infection. The biological mechanisms responsible for the typical speedy resolution of a cold have yet to be well established. Symptoms generally peak 2 to 3 days after the initiation of infection, in laboratory studies, and last for about a week, although

specific symptoms may vary in their kinetics.[21] Although specific antibody levels rise in response to rhinovirus infection, raising the possibility that local or systemic antibodies may play a role in the resolution of the infection, the increase in specific antibody is generally not seen until after symptoms have already resolved.[21] This increase may be more important in protecting against the next infection than in resolving the current one. As has been well established for other viral infections, cellular immune defenses are also likely to play a critical role in recovery from rhinovirus infection.[7] Although the literature examining the role of cell-mediated mechanisms in the resolution of rhinovirus infections is not entirely consistent, there have been several reports of changes in lymphocyte numbers and activity during the early stages of infection.[1] To take just one pertinent example, the in vitro levels of mitogen-stimulated interleukin-2 and interferon produced by lymphocytes isolated from the blood of subjects infected with rhinovirus have been reported to be inversely correlated with the duration of their infection.[22] If continuing research confirms the importance of such cell-mediated responses to the resolution of rhinovirus infections, it will be important to formally explore the possibility that alterations in these responses may mediate the relations between psychological factors and infection. As yet there is no direct evidence of this mediation.

Step 6: The generation of immunologic memory. As noted previously, rhinovirus infections, with or without symptoms, typically result in a robust antibody response to the particular virus, which provides the individual with lasting protection against future infection with the same virus.[7] Therefore, psychological influences on the magnitude of the antibody response to a given rhinovirus infection might have a long-term impact that would not be revealed until the individual was again exposed to that particular virus, when lower levels of antibody would increase vulnerability. Although this possibility has yet to be directly investigated in individuals undergoing infection with rhinovirus, recently there have been a few studies of psychological influences on antibody responses to routine medical vaccinations that provide some indirect support.[23] For example, Glaser and colleagues found that individuals who had the strongest antibody response to their first hepatitis B inoculation (i.e., they seroconverted) had reported lower levels of anxiety and tension at the time of the vaccination than those individuals who did not seroconvert.[24] It will be of particular interest in future studies to examine the relations between psychological influences on primary and secondary (memory) immune responses to antigenic challenge.

Summary

My purpose in focusing on the common cold in this commentary is not so much to convey the details of possible pathways by which psychological factors could influence this particular illness, but rather to emphasize that there *are* details. And, as the saying goes, "The devil is in the details." The pathways that will be found to mediate psychological influences on the common cold (e.g., mucosal immunity, local neural regulation of nasal secretions) may be quite different from those found to mediate effects on, say, systemic bacterial infections. Failure to consider the *specific* pathogenic mechanisms involved in a *specific* illness may result in a counterproductive oversimplification of our thinking about the psychoneuroimmune mechanisms that may be involved in that illness.

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Chapter 10

PSYCHOLOGICAL STRESS AND UPPER RESPIRATORY ILLNESS

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INTRODUCTION

Accumulating evidence from both naturalistic and experimental studies indicates that psychological stress can affect upper respiratory illness (URI). This literature has recently been reviewed in considerable detail by three separate research groups with complementary perspectives.[1-4] In their reviews, Boyce and Jemerin focused on infectious illness in children, emphasizing the role of individual differences in susceptibility.[1,2] Cohen and Williamson reviewed the broader literature on stress and disease in humans, with an emphasis on psychological factors.[3] Peterson and colleagues, on the other hand, reviewed both human and animal studies, with an emphasis on biological factors.[4]

Our purpose in this chapter is not to present another exhaustive review of the literature on psychological stress and URI, but rather to highlight some of the important issues for this area of research, as well as research conducted since those previous reviews. Throughout the chapter, our focus will be on human URI. We will usually focus our consideration of URI to the common cold, both because colds are the most common URI, and because colds have been the most frequent subject of studies on psychological stress in URI.

This chapter is divided into five sections. The first section provides a brief introduction to the various ways stress has been conceptualized in psychobiological and health studies. The second section provides an overview of upper respiratory disease, including etiology, pathophysiology, and immune defenses. The third section outlines the steps in the pathogenesis of URI where psychological stress could conceivably exert its influence, and possible mechanisms of such stress effects are discussed. The fourth section provides illustrative examples, organized by study design (cross-sectional, longitudinal, and viral exposure), of studies that have examined the association between stress and URIs. The fifth section provides a summary and recommendations for future research.

WHAT IS PSYCHOLOGICAL STRESS?

There has been considerable debate concerning the definition of psychological stress.

At least four different ways of conceptualizing stress have been discussed.[5-7] 1) The *environmental approach* defines stress as significant, objective changes in the environment. Some environmental definitions are based solely on the degree to which events require readjustment in one's lifestyle, whereas other definitions are based on the extent to which events are upsetting. Examples of this approach are the studies of major life events (e.g., death of spouse, change in employment, major purchase) and daily minor events (e.g., argument with spouse, problem at work, issues with children). 2) The *appraisal/emotion approach* defines stress as judgements of a situation as challenging or threatening (appraisal approach) or as the experience of negative emotions, such as anxiety or sadness (the emotion approach). This conceptualization hinges on psychological reactions to environmental events. 3) The *physiological approach* defines stress in terms of relatively stereotypic alterations in physiological processes. Examples of stress defined this way include activation of the hypothalamic-pituitary-adrenal axis (e.g., evident in increased plasma cortisol concentrations), or activation of the autonomic nervous system (e.g., evident in increased blood pressure). 4) The *integrative approach* defines stress as certain combinations of the above elements. An example of this approach is Lazarus' transactional model of stress and coping.[8] According to this model, stress is the result of a unique interaction of environmental change, specific appraisals, and coping efforts to modify emotions and/or problems. It is conceptualized as a temporally changing process (hence, transactional), which includes feedback from later processes that can, in turn, affect earlier processes.

A common characteristic of these conceptualizations of stress is that an external stimulus of some sort (a stressor) is always thought to be involved. It is also commonly presumed that stress has the potential to result in a negative health outcome.[7] In the review that follows, we have included studies that examined relations between URI and either some external stimulus (stressor) or some change in appraisal or affect. For the purpose of this review, defining stress as a physiological response seems, to us, conceptually too closely related to URI. We have limited our review to studies of clear environmental changes that are perceived as unpleasant or stressful. We have not included articles of more general psychological states (e.g., personality) which may have their own effects on URI.

UPPER RESPIRATORY INFECTION

Background

Nationwide annual surveys regularly indicate that URI is the single most common cause of physician visits and missed days of work among all acute medical conditions.[9] In 1990, Couch[9] estimated that the common cold and influenza accounted for 165 million significant illnesses, resulting in an average of 3.2 days of restricted activity and 1.6 days in bed; half of those illnesses received medical attention. It has been estimated that upper respiratory symptoms precipitate as many as 14% of all visits to physicians.[10] The common cold has been calculated to be responsible for 30 million lost days at school and work each year; to cost $3 billion for physician office visits; and to cost $2 billion for over-the-counter drugs.[11] Common colds, although not serious medical conditions, thus pose a major public health problem.[10]

The incidence of common colds is highest in infants and children, who suffer from four to eight colds each year; adults typically get two to five colds, except in households with children, where the incidence is higher.[12] Indeed, children's noses have been characterized as

the chief reservoir for cold viruses,[10] with dissemination into the broader community occurring as infection moves from school to home, where parents become infected.

The viruses responsible for colds (see below) are transmitted by airborne droplets and aerosol (e.g., by sneezing), as well as through environmental contamination with virus-laden nasal secretions (e.g., by touching the eyes or nose with contaminated fingers).[12] For example, rhinovirus in nasal secretions of an infected individual has been demonstrated to be easily spread by the fingers to a variety of common household objects (e.g., doorknobs), where it can survive for several hours, serving as a source of infection.[13]

INFECTIOUS AGENTS

Rhinoviruses are the most common cause of the common cold.[13] Based on survey studies with samples collected for viral identification, rhinoviruses have been estimated to be responsible for 40 to 60% of all colds in adults.[9] The virus can either be identified in nasal secretions from the infected individual or by the presence of specific antiviral antibodies in serum or nasal secretions following infection.[13] More than a hundred different types of rhinoviruses (serotypes) have now been identified.[13] Coronaviruses (3 types), which are technically more difficult to identify, have been estimated to be responsible for another 20% of colds in adults and perhaps more in children.[9] Other viruses known to be associated with classic cold symptoms (e.g., rhinorrhea) include the influenza viruses (3 types), parainfluenza viruses (4 types), and respiratory syncytial virus; if not contained by host defense mechanisms, these viruses typically go on to cause more serious illness and associated systemic symptoms (e.g., fever).[9]

SYMPTOMS OF INFECTION

The multitude of different upper respiratory viruses, reviewed above, all typically cause a strikingly consistent constellation of symptoms including rhinorrhea, nasal obstruction, sneezing, pharyngeal discomfort, and cough, which are familiar to all of us as a common cold.[9,10,13,14] It should be noted, however, that for reasons that are as yet obscure, about a third of all verified rhinovirus infections have been found not to result in symptomatic illness (i.e., in clinical colds).[13] For many adults symptoms begin with a dry, "scratchy," or sore throat, soon followed by a watery nasal discharge, inflammation of the nasal mucosa, and sneezing.[12] Some systemic symptoms such as general malaise and myalgia may be evident, but fever is rare.[12] After one to three days, nasal obstruction is common, the nasal secretions thicken and are no longer clear.[12] In infants, fever and other systemic symptoms including anorexia, vomiting, and diarrhea are more commonly associated with colds.[12] Symptoms typically begin to decline within a few days and last for about a week, although in some cases they may linger for as long as a month.[15]

Confirming the commonality of symptoms across different infectious agents, a recent study conducted at the Common Cold Unit in England conducted detailed symptom assessments of viral shedding following exposure of healthy subjects to several different URI viruses.[16] Three different rhinoviruses, a respiratory syncytial virus, and a coronavirus were administered to quarantined volunteers, and symptoms were carefully monitored over the next several days. Although there were some modest differences in the rapidity with which symptoms developed, suggesting differences in the incubation period, by two to three days after

the viral exposure, symptoms peaked. There were no major differences in the pattern of symptom development across the five viruses.

The ubiquity of this symptom constellation across different viruses suggests common pathogenic mechanisms (see below) and raises the possibility that these symptoms may confer an adaptive advantage to the infected individual. Ewald[17] has theorized that from an evolutionary perspective, symptoms of infection can be viewed as either: 1) adaptations of the pathogen to increase its reproductive success; 2) adaptations of the host to defend against the pathogen; 3) "side effects" of the infection that do not serve adaptive functions for pathogen or host. Which role is played by the symptoms of a common cold has yet to be determined.

ASSESSMENT OF ILLNESS

As might be expected from the discussion above, the literature includes two ways of assessing URIs: the presence of the symptom syndrome (clinical cold) or the presence of an infection, verified by isolation of virus from nasal secretions or by increases in specific antibody titers. As will be discussed below in the section on viral exposure studies, individuals can manifest an infection yet not demonstrate the clinical syndrome. Although one might demand that both infection and syndrome be present as a conservative definition of URI, this would virtually eliminate the study of URI in natural observation studies. The reason for this is that it is difficult to confirm viral infection when the particular virus is not known, which is the typical case in epidemiological studies of URI syndromes. Viral exposure studies can, on the other hand examine both clinical syndromes and infection (because the strain of virus is known and can be specifically tested for).

IMMUNE DEFENSES AND THE PATHOGENESIS OF RHINOVIRUS INFECTION

Neither the pathogenesis of infection nor the relevant immune defenses is well understood for any of the more than 200 distinct viruses known to infect the human upper respiratory tract.[9] In the discussion that follows we will again focus on the rhinoviruses, the pathogenesis of which has been under increasing scrutiny in a series of experimental inoculation studies.[12]

Besides avoiding exposure to the rhinovirus, the best established initial immune defense against infection is the presence of protective levels of specific antibody for the virus as a result of previous exposure.[13] An early study by Hendley and colleagues[18] revealed an inverse relation between individuals' levels of serum neutralizing antibodies to the challenge rhinovirus and their subsequent susceptibility to experimental infection. More recent research, using a more sensitive ELISA assay, has continued to indicate the protective value of specific antibody to the challenge virus in either serum or nasal secretions prior to experimental inoculation.[19] Immunoglobulin in nasal secretions, predominantly secretory Immunoglobulin A (sIgA), but also including Immunoglobulin G (IgG), is thought to reduce the risk of infection by interfering with viral attachment to the epithelial surface.[20] It should be noted that the nasal mucosa has a wide range of nonspecific defense mechanisms that are also likely to play a preventative role; not the least of these is the outer layer of the mucous blanket itself, which by ciliary action transports particles to the posterior pharynx where they are swallowed.[21]

Although the protective role of secretory antibody at the mucosal surface is widely accepted, the relative importance of secretory and circulating antibody is still debated, with some investigators arguing that circulating antibody may be responsible for long lasting immunity.[22] It is also too early to rule out possible contributions of cellular defenses, whose role at mucosal surfaces has received little attention.[23]

Viral infection is, beyond a doubt, the critical initiating step in the pathogenesis of a clinical cold, but the chain of events leading from infection to the manifestation of symptoms has yet to be fully elucidated.[24] Several lines of evidence suggest that the virus itself is not directly responsible for symptoms. First, it is quite possible to be infected and have no symptoms. Typically, in both experimental studies and field studies, a third of the subjects with confirmed infections have no symptoms.[13] Second, histological studies with light and/or electron microscopy have found that rhinovirus infection, unlike influenza, does not cause damage to the nasal epithelium.[25] Third, although symptoms tend to be most severe when viral shedding is at its peak (e.g., day 2), shedding typically continues for several days after symptoms have resolved.[25] Fourth, accumulating evidence indicates that viral infection triggers the release of inflammatory mediators, which in turn cause the symptoms.[13]

Increased levels of kinins (e.g., bradykinin and lysylbradykin) have been found in the nasal secretions of symptomatic but not asymptomatic individuals, following both natural and experimental infection with rhinovirus.[26,27] Consistent with the possibility that kinins may play a role in symptomatology, provocation experiments have shown that nasal application of bradykinin causes rhinorrhea, nasal obstruction, and sore throat in volunteers.[28] In addition to their direct effects on vascular permeability, a major contributor to nasal secretions early in the course of a rhinovirus infection,[29] kinins are thought to affect local secretory responses and pain by stimulating nerve fibers in the nasal mucosa.[28,30] Although neural regulation of nasal secretions is complex and, as yet, poorly understood, both cholinergic and sympathetic nerves are thought to regulate the passive diffusion of plasma proteins, as well as active secretions (including sIgA) from serous and mucous glands.[21,31] Psychological influences could thus affect the secretion of kinins or the neural regulation of nasal secretions.

Unlike allergic rhinitis, no increases in histamine or prostaglandin D2 have been found in nasal secretions following rhinovirus infection, suggesting that mast cells may not play a role in the symptoms of a cold.[26,27] The severity of symptoms has been found to be correlated with an increase in the numbers of lymphocytes and neutrophils in nasal secretions.[25,32] Increased numbers of neutrophils have also been histologically documented in biopsies of the nasal mucosa of symptomatic individuals.[25] One possible explanation for these effects is suggested by a recent study indicating that nasal lavage fluids from symptomatic subjects contained significantly higher levels of interleukin-1 (IL-1) than asymptomatic, or sham-infected, subjects.[24] It is tempting to speculate that this IL-1 reflects the activation of local cellular defense mechanisms, but IL-1 is known to be secreted by a wide variety of nonlymphoid tissues, including nasal epithelial cells.[33,34] In any case, local secretion of IL-1 could upregulate a wide range of both local and systemic cell-mediated immune defenses.[33]

The mechanisms responsible for recovery from rhinovirus infection are not yet clear. A role for local and/or systemic neutralizing antibody cannot be ruled out, although in most studies increased levels of specific antibody have not been detected until the illness has resolved.[13,15] As with other viral infections, cellular immune defenses may play an important

role in recovery, although local secretion of interferon may also be involved.[13] Although direct evidence for cell-mediated recovery mechanisms is lacking, there is some circumstantial support. As noted above, the number of lymphocytes and neutrophils in nasal lavages from infected subjects is significantly elevated within the first few days after experimental infection with RV25, raising the possibility that leukocytes in the nasal mucosa may play a role in resolving the infection.[32]

There is also some initial evidence consistent with the possibility that systemic cellular responses may play a role in resolving the infection. For example, three days after infection with the same rhinovirus serotype (RV25), Levandowski and colleagues[32] found decreases in peripheral blood lymphocyte numbers (including T cells, but not B cells); the decreases in cell numbers were inversely correlated with the number of days of viral shedding. Three days after infection with a different rhinovirus (Hanks), Hsia and colleagues[35,36] found no change in lymphocyte numbers, perhaps reflecting differences in the kinetics of infection which have been demonstrated across different viruses.[14,16] After five days, however, these investigators[36] found significant increases in lymphocyte numbers (including T cells, but not B cells). *In vitro* assessment of isolated peripheral blood mononuclear cells (PBMC) revealed increased levels of PHA-stimulated interleukin-2 and interferon production, which were inversely correlated with the duration of viral shedding. Confirming a previous report,[37] these investigators also found that the *in vitro* proliferative responses to the challenge virus were also increased following infection, as was natural killer (NK) cell activity.[36] *In vitro* proliferative responses to the challenge virus were also found to be increased following experimental infection (RV39) in another recent study,[38] but these investigators found reduced levels of NK cell activity in peripheral blood mononuclear cells collected seven days after infection.

All of these studies can be viewed as consistent with the possibility that cell mediated responses may play a role in recovery from rhinovirus infection, but none provides proof. The immune mechanisms responsible for recovery from rhinovirus infection remain to be determined. Although it is tempting to theorize that mucosal immune defenses must be more critical in resolving what is widely accepted as a localized infection,[13] systemic responses to rhinovirus may also play an important role. Indeed, there may be a false dichotomy in this thinking. Optimal recovery will likely depend on local and systemic responses working in concert.

HOW COULD PSYCHOLOGICAL STRESS AFFECT URIs?

There are several points in the pathway of pathogenesis where stress could affect URI, as is schematically shown in Figure 1. First, psychological stress may alter exposure to virus in some way. For example, people experiencing high stress levels may cope with the stress in ways that encourage exposure (Arrow #1). One method of coping with stress is called seeking social supports,[39] and it involves procuring practical advice and/or emotional support from others. This contact with others, some of whom may be shedding URI virus, could increase exposure to pathogens.

Lowered host prevention mechanisms to initial viral exposure is a strong possibility for mediating stress effects (Arrow #2). There is substantial research showing that psychological stress affects immune system function,[40] including many of the immune components previously discussed (e.g., sIgA). Stress may alter immunity by affecting behaviors such as sleep patterns,

eating, consumption of alcohol medication use, and exercise.[41] It has also been shown that stress can affect immunity via direct neural connections and/or hormonal changes (reviewed in previous chapters).

Similar to host prevention mechanisms, the immune system is thought to play a role in controlling viral replication in the nasal mucosa (Arrow #3). Both cellular and humoral systems probably contribute to controlling viral replication and both are likely to be influenced by the same stress-related factors mentioned for host prevention mechanisms.

Fig 1. Possible ways that psychological stress could affect URIs

Clinical syndrome refers to the constellation of symptoms associated with URIs (mentioned above). It is important to note that URI does not always lead to clinical syndromes; as noted earlier, for rhinovirus only about two thirds of those infected (confirmed by viral shedding and/or raised antibody titers later) manifest symptoms. There is currently no explanation for this discrepancy, but clearly there must be individual differences in the physiological processes that affect symptom expression. Psychological stress may contribute to the individual differences by affecting the underlying processes responsible.

Recovery from a clinical syndrome usually takes several days. Stress could potentially influence the processes that are responsible for determining the duration of infection and symptoms (Arrow #5). In addition to physiological processes, stress could influence patients' use of medications.

Finally, after the experience with URI viruses, the immune system will be better poised to defend against future infection through both specific (e.g., secretory antibody response) and nonspecific mechanisms. Psychological stress has been shown, for example, to affect antibody response to vaccination.[42] It may be that psychological stress influences the magnitude of this secondary response.

Although there may be other routes by which psychological stress influences URI, these six routes are likely candidates. As will be evident from the discussion below, many of these routes have not yet received any research attention.

REPRESENTATIVE STUDIES EXAMINING THE ASSOCIATION BETWEEN STRESS AND URIs

Cross-sectional Field Studies

A number of studies have been conducted exploring associations between naturally occurring stressors and URI symptomatology. Some of these studies examined objective indices of URI infections as well. These studies provide support for the hypothesis that stress is associated with URI, yet clearly much research remains to be done.

Graham *et al.*[43] reported a survey of 2,618 children and their families in Australia. The survey examined the association between the mothers' stress and URI symptoms in children. Families were selected for the study if the proband (the child) fell into either the upper or lower quintile of the distribution of URI symptoms over the last year. Mothers' stress was assessed by a combination of scores on a major life event checklist, a daily hassles checklist, and an emotional distress scale. Mothers were labelled as stressed if their scores on all three measures were above the median. These procedures yielded a sample of 255 children with frequent URIs and 227 with infrequent URIs. Their average age was about 2.5 years. Children whose mothers were in the high stress group were four times as likely to be in the high URI group than those whose mothers were in the low stress group. Although other risk factors significantly contributed to a model developed by the investigators to predict URI group membership (e.g., chest illness in the child's first year of life was a strong predictor), the mothers' stress level was the second most powerful predictor of URIs. The investigators acknowledge the bidirectional interpretations that are consistent with this data, namely, that mothers of ill children may be stressed for that reason or that their stress causes increased illnesses. Regarding the latter hypothesis, it may be that a decrement in family hygiene due to the mother's stress or enhanced susceptibility of children could be operative.

A negative finding was shown in a study notable for its verification of infection. Clover *et al.*[44] studied 281 adults and children during an influenza outbreak. Sixty six subjects developed verified influenza: 35% of the children and 17% of the adults. A major life events inventory was administered yet showed no association with influenza status. However, a measure of family cohesion was negatively related to infection.

LONGITUDINAL FIELD STUDIES

Longitudinal studies have followed subjects on more than a single occasion. They have many of the same methodological weaknesses as cross-sectional field studies. The studies are correlational and, hence, cannot rule out third variable explanations for observed relations. However, the repeated measurements of both stress and URI allow for predictions of URIs from levels of stress reported *before* URIs are reported. Such prospective prediction allows stronger statements about causal relationships between stress and URI. Despite this strength, data from longitudinal studies have often not been analyzed in ways that capitalize on prospective prediction.

An excellent example of an early longitudinal field study is one that was conducted by Roghmann and Haggerty.[45] In this 1973 study, 512 families were monitored over a 28-day period by mothers. Using a health diary, mothers recorded significant events that were perceived as stressful (e.g., losses, arguments, financial problems), as well as health symptoms in each family member and his or her medical care utilization. Unlike many survey studies, these investigators utilized the longitudinal data in sophisticated ways, which served as a model for later studies of stress and health. Although the authors did not specifically analyze URIs, they state that most illnesses included fevers, coughs, headaches, and "colds." It is thus very likely that the vast majority of the illnesses analyzed in this study were URIs.

Considering all of the members of families studied, a total of 71,346 person-days were examined. On a day-by-day basis, the investigators found that 30% of the days could be characterized as stressful, but only 10% were found to be in the upper range of the stress score. A health complaint was reported by mothers about themselves on 25% of days, and for their youngest child on 17%. Same-day analyses showed that the probability of a mother having an illness doubled when stress was present on that day versus when it was not present; a 50% increase was observed for the youngest child. However, the most powerful analyses were based on the notion of stress and illness *episodes*. In accord with the commonsense notion that difficult times tend to stretch over multiple days and that the same is true for illnesses, the authors analyzed the correspondence between episodes of stress and illness. Importantly, they analyzed the data such that lagged associations would be evident: that is, stress episodes preceding illness episodes and vice versa. They found a 250% increase in illness episodes following stress episode onsets compared to what would be expected by chance, suggesting a causal relation.

In another of the earlier studies of URI in children, Boyce *et al.*[46] repeatedly assessed 58 children in a daycare setting. Children (average age 4 years) were observed on a daily basis on weekdays for an entire year, during which time all illnesses were assessed by a nurse practitioner. Additionally, biweekly nasopharyngeal cultures were taken; cultures were also taken at the start of each illness. At the end of the year, parents completed several questionnaires, including a major life events inventory for events in the child's life and a

questionnaire about weekly family routines. Observational data yielded several measures of illness: frequency, average duration, average severity, and a composite measure (days of illness times average severity). When age, sex, race, family income, and family size were controlled, results indicated that the child's life event stress was associated with illness duration. More life stress was associated with longer illnesses. Interestingly, life event stress interacted with family routine such that those children with high stress and strong family routines had more severe illnesses than other children. It is important to note that stress was not associated with frequency of illness. In contrast to the previous study, these results are less convincing since prospective analyses (lagged relations) were not computed.

In the 1980s a number of studies examined the associations between minor symptomatology and two types of stress: major life events and daily events/hassles. At issue was not the nature of the association between stress and illness, but the then recent emergence of minor event and hassle checklists as a way of assessing stress. Therefore, the goal of these studies was to compare how well minor versus major events could predict symptomatology. Since the focus was not on the symptoms, it is often not clear exactly what sorts of symptoms respondents reported. Importantly, the concept of symptom episodes was not part of the methodology, making it difficult to know what a total symptom score meant (several individual days of symptoms or a few long episodes, etc.). Despite these shortcomings, several of these studies demonstrated that major life events and minor events both predicted symptom rates, with the edge going to minor events.[47,48]

Stone, Reed, and Neale[49] conducted a study capitalizing on the prospective associations of daily data collected in a longitudinal manner. Seventy nine community-dwelling, middle-aged, married males were studied for 84 consecutive days. An important feature of this study was the careful assessment of daily events. Husbands completed the daily event questionnaire about themselves each evening and their wives confirmed the reports of husbands' events (prior work had shown that this procedure improves event reporting). Another important design feature of this study was that questionnaires were completed on a daily basis and mailed to the investigators on the following day; this procedure has been shown to reduce the possibility that subjects complete multiple days at one sitting.[50]

This study following the conceptualization of URIs used by Roghmann and Haggerty,[45] isolating episodes of symptoms with symptom clusters consistent with a cold or flu (unlike Roghmann and Haggerty, however, no single-day episodes were allowed). The frequency of desirable and undesirable daily events was examined for several days prior to the onset of URI episodes. For control periods, days that did not precede URIs (matched for day of the week as well) were selected from the same subject. An increase in undesirable events and a decrease in desirable events were observed in the three to five day period prior to URIs relative to control days. Notably, there were no differences in event report, either desirable or undesirable, one or two days before URI onsets. This pattern of data makes it less likely that there was a reporting of subsyndromal symptoms, not recognized by subjects, since the most likely period for such an effect to be observed would be immediately before the URI onset.

Three additional studies have extended the Stone, Reed, and Neale[49] findings. Evans, Pitts, and Smith[51] replicated the dip in desirable events preceding URIs, using a similar methodology to that of Stone *et al.*[49] However, these investigators did not observe an increase in undesirable events prior to the onset of URIs. In an independent study, Evans and

Edgerton[52] again found a decrease in the frequency of desirable events before URIs, and this time they observed a trend for an increase in undesirable event frequency. Finally, Stone, Porter, and Neale[53] examined the same association in yet another longitudinal, daily diary study. No replication of either a dip in desirable events or a peak in undesirable events was observed. A comparison of the methods and analytic techniques employed in all four of these studies can be found in Stone, Porter, and Neale,[53] but suffice it to say that the bulk of the evidence is in favor of an effect of fewer desirable events and, less strongly, more undesirable events prior to URIs.

VIRAL EXPOSURE STUDIES

Naturalistic studies have the advantage of ecological validity[54] because subjects are exposed to "real" levels of stressors and naturally occurring exposures to pathogens. A disadvantage of these designs is that determining causal pathways is difficult because stressor and pathogen exposures are not controlled. Viral exposure studies can address these problems. These studies typically manipulate exposure to selected pathogens and can manipulate stressor levels as well, unlike field studies where the pathogen responsible for the URI symptoms is usually not identified (in part, because any of scores of viruses could be responsible). We should note, however, that given the expense of these types of studies, only a handful have been conducted, and these examined a very small selection of URI viruses.

One of the first studies exploring stress and experimentally-induced URI came from the Common Cold Unit (CCU) in England.[55] The CCU conducted a series of studies designed to understand the pathophysiology of the common cold by inoculating healthy individuals with live cold viruses. In 1977, Totman *et al.*[55] explored whether cognitive dissonance produced by a difficult decision paradigm was related to the incidence of infection or to cold symptoms in individuals exposed to either of two rhinoviruses. Although stress was not explicitly assessed, subjects who experienced decision making may be thought of as being stressed by the procedure (an interpretation advanced by the authors). After controlling for pre-existing antibody levels to the challenge viruses, "stressed" subjects had significantly higher levels of symptoms, but no differences in the incidence of infection or the amount of shed virus in nasal secretions.

A second study by Totman[56] from the CCU paradigm explicitly examined life event stress. In addition to the life event checklist, an interview fashioned after Brown's method[57] of objectively recording major experiences was used to create several stress indices. These included the SEI, assessing the time-adjusted impact of events, the SDI, assessing the total magnitude of life events, the TLI, assessing changes in "goal-directed" activities due to events, and the TCI, another measure of change in activities due to events. Measures of extroversion and neuroticism were also administered. After controlling for preantibody status prior to the experimental inoculation with the viruses, only the TLI was associated with total symptom score. Only the TCI was associated with amount of viral shedding. These relationships were complicated by the overlap between the stress measures associated with response to viral exposure (TLI and TCI) and extroversion, which had the strongest association with both symptoms and viral shedding. Regression analyses controlling for the overlap did, however, show that the TCI had an independent effect on shedding over that explained by extroversion.

More recently a landmark study by Cohen *et al.*[58] also at the CCU showed that levels of stress prior to inoculation with live virus were associated with susceptibility to and clinical syndromes of several URI viruses. In this study, 394 volunteers were exposed to one of several URI-inducing viruses. A psychological stress index was created by combining three separate stress scales that were administered upon entry to the CCU: a life events inventory, the Perceived Stress Scale, and a negative affect scale (for the past week). After controlling for pre-existing antibody levels to the viruses and for a variety of subject variables (e.g., age, sex, education, allergic status, weight, season), the association between the stress index and two outcomes was examined. Outcomes were: 1) the percentage of subjects who became infected with the experimental virus, as indicated by isolation of the shed virus or by increase in antibodies to the virus, and 2) the percentage of subjects who manifested clinical cold syndromes. For infection, there was a linear rise in proportion of subjects infected as stress levels increased. At the lowest stress levels, less than 75% of the subjects were infected, whereas at the highest stress levels, about 90% were infected. A parallel pattern emerged for the proportion of subjects with colds: at the lowest stress levels, under 30% had colds, while at the highest levels, about 45% had colds. This data provides some of the strongest evidence in support of the hypothesis that psychological stress affects URI.

A further analysis of the data from the Cohen, Tyrrell, and Smith[58] study explored relationships between individual components of the stress index and susceptibility to URI.[59] Analyses in this paper indicated a somewhat surprising set of associations. Only the life event measure was a significant predictor of clinical colds. In contrast, negative effect and perceived stress were significant predictors of infection.

A study by Stone and colleagues[60] essentially replicated the life event findings of the Cohen study in a smaller sample. Seventeen college undergraduates, all of whom had no pre-existing antibody titers to the experimental virus, were experimentally inoculated with a rhinovirus. At the outset of the study, subjects completed a life event inventory, resulting in a stress score reflecting the total number of events experienced in the last year, and a mood assessment. Because prior to entry into the study subjects were screened for having no antibody to the experimental virus, all subjects became infected after viral exposure (unlike the Cohen study where some individuals did have pre-existing antibodies to the experimental agents). Subjects were classified by whether or not they had a clinical cold: 12 of 17 (71%) did. Subjects who did not develop colds had fewer life events (2.6 vs. 7.3) than those who developed colds. Interestingly, when events were categorized according to subjects' perceptions, subjects without colds had fewer negative (nonsignificant) and more positive (significant) events. There were no differences in the groups of subjects in terms of negative or positive effect (an alternative way of conceptualizing stress).

PHYSIOLOGICAL MEDIATION OF PSYCHOLOGICAL STRESS AND URIs

With rare exception, the studies reviewed above have not directly examined possible mediating pathways that could be responsible for the associations between stress and URI. This comment should not be taken as criticism. It is appropriate that early investigators focus on establishing phenomenon before attempting to explain how it works. The validity of the demonstrated relations between psychological variables and URI is not compromised, after all,

by our current lack of knowledge concerning the mediating mechanisms. On the other hand, consideration of possible mechanisms might help to explain some of the apparent anomalies in the present literature and suggest improved strategies for detecting psychological influences in future research. For example, are there plausible mechanism(s) that could account for the apparent selectivity of the effects of life events on colds due to rhinovirus infection? As reviewed above, differences in life events were not found to predict which individuals would become infected following experimental inoculation with rhinovirus, but did predict who would develop the symptoms of a cold.[59,60]

As we discussed above, there are several possible pathways that could link psychological variables with URI. The problem is knowing where to begin. We present one line of research exploring a possible pathway that may mediate the effects of psychological stress on URIs.

Some of the strongest evidence reviewed above supporting the association between stress and URIs was from prospective daily diary studies. There have been two studies which have examined a potential immunological mediator of stress and URIs, secretory IgA antibody, which was mentioned in the section on pathogenesis of URI.[62] We focus here only on the studies using specific sIgA antibody to a known antigen and bypass studies that have examined stress and nonspecific sIgA protein, because it is not clear that total sIgA protein is a meaningful index of immunological protection. It is more likely that specific antibody to a known antigen behaves in an analogous manner to URI pathogens.

The immunologic model used in both studies[61,61] involved repeated challenge with a (relatively) novel protein for participants, purified rabbit albumin. Every morning for a number of consecutive days, subjects ingested 100 mg of albumin. Specific antibody responses were monitored via nightly saliva samples obtained directly from the parotid gland with a Curby cup. An index of antibody activity was obtained by dividing sIgA activity to the albumin (obtained through ELISA) by overall levels of sIgA protein (obtained through RID), in order to control for salivary flow rates.

The stressors differed in the two studies: in the first it was affective states (negative and positive moods) and in the second it was the number of undesirable daily events (and the number of desirable daily events as well). In both studies, effects of stress on sIgA antibody to the albumin were demonstrated. In the first study,[61] thirty dental students were studied over an 8 week period, 3 times per week. Days with high negative mood had lower levels of specific antibody activity compared to days with low negative mood. Opposite findings emerged for days with high and low positive mood; namely, high positive mood days were associated with higher levels of specific antibody. (Notably, these associations were not observed for total sIgA protein levels.)

The second study examined 96 community-dwelling, married males who participated for 12 consecutive weeks.[62] On a daily basis they recorded undesirable and desirable events as well as mood; an evening saliva sample (as described above) was also taken to examine sIgA response to the ingested antigen. On days with relatively high numbers of undesirable events, lower levels of sIgA antibody were observed. Conversely, days with higher numbers of desirable events were associated with higher levels of antibody. In addition to concurrent daily analyses, lagged analyses, where event levels on one predicted antibody on a latter day, were also computed. Surprisingly, the effect of undesirable events was limited to the same day, whereas the effect of desirable events appeared to last for two subsequent days. Additional analyses

explored the possibility that the effects of events on specific sIgA response were mediated through shifts in mood.[63] These analyses were consistent with the hypothesis: effects of both desirable and undesirable events were largely, although not exclusively, mediated through their effects on mood.

SUMMARY

This chapter has highlighted the substantial evidence from field studies and experimental viral exposure studies which suggest an association between psychological stress and URI. Overall, the majority of the studies found significant relations between stress and URI. The strength of the cross-sectional field studies is their epidemiological nature: large numbers of subjects were studied for an impressive number of days. Many of these studies focused on URIs in children, an important subject population given the high prevalence of URIs in this age group and their important role as a reservoir of infection. An additional strength of the prospective, longitudinal field studies is their attention to the timing of stress relative to URI. These studies generally show that stress precedes the onset of URI episodes. For example, several studies have found a significant increase in minor stressors a few days before the onset of URI symptoms. Of course, it is difficult to confirm infection in field studies. Exquisite control of viral exposure and intensive monitoring of symptoms (including objective measures such as mucosal weight) are strengths of the viral exposure studies. However, it must be noted that stress was not explicitly manipulated in these studies. The isolation of subjects that is required for these studies could be considered a stress-reducing intervention, as there may be fewer minor stressors compared to those experienced in the outside world. From the viewpoint of the psychological independent variable, these viral inoculation studies are not true experimental designs. As with the field studies, the relations between psychological stress and URI have been correlational. Nevertheless, the viral exposure studies represent the strongest evidence that stress can affect infection as well as symptoms of infection. It is particularly noteworthy that two independent studies have raised the possibility that the *symptoms* of URI may be affected by different types of psychological stress than the *incidence* of infection; these apparently selective effects can be best investigated in further viral inoculation studies.

We outlined several ways that psychological stress could affect URI, including influences on viral exposure, initial host susceptibility, viral replication, the clinical syndrome, recovery mechanisms, and the enduring protective immune response. Although there are many possible mechanisms by which stress could affect URIs, few have been examined. This focus is quite appropriate from the standpoint of public health issues. Regardless of the underlying biological mechanisms, significant effects of stress on the symptom syndrome in infected individuals could have a major impact on societal costs. Initial evidence indicates that stress may play a role in determining which infected individuals develop symptoms. Recall that nearly a third of those infected do not develop the clinical syndrome of a cold. These symptom-free individuals are unlikely to seek medical attention or to purchase medications. From a public health perspective, psychological effects on the incidence of infection are also important, of course. In addition to increasing the number of individuals with symptoms (who would then seek treatment), increased rates of infection due to stress could increase the pool of contagious

individuals, thus furthering the spread of the virus throughout the population.

Although one can cautiously conclude from the literature that there is an association between stress and URI, a number of issues remain to be investigated before we can fully understand the relations. Five of these were highlighted in the review by Cohen and Williamson.[3] (1) *Little is known about how the timing of the stressor and viral exposure influence the development of URI.* Some evidence suggests that stress occurring after viral exposure may increase susceptibility, whereas mixed findings (increased and decreased susceptibility) have been reported when stress occurs prior to viral exposure. Temporal relations clearly go uncontrolled in naturalistic studies, and are more difficult to determine, as no information is available about the timing of subjects' exposure to virus. Such temporal issues could be addressed in viral exposure trials. (2) *Little is known about differential effects of acute (shorter-term), chronic (longer-term), and repetitive stressors.* The health psychology literature suggests that chronic stress may have particularly pernicious effects on health, so distinctions among the duration and patterns of stress should be researched for their effects on URI. However, additional conceptual work may be needed to define stressors according to a chronicity dimension. (3) *True experimental studies of stress exposure should be conducted (namely, where subjects are randomly assigned to stressor conditions).* Although viral exposure studies appear to be experimental (because they have a high degree of experimenter control over the situation), as mentioned above, they generally are not because the independent variable, stress, is not manipulated. A number of experimental stress procedures have been developed and used extensively in cardiovascular reactivity and psychoendocrinology research. These procedures could easily be adapted for use in conjunction with viral exposure trials, and would increase confidence in the causal processes suggested by observational studies. (4) *Little is known about the biological pathways that may be responsible for the association between stress and URI.* We have outlined several points in the process from viral exposure through resulting protective memory response after the infection where stress could affect URI. As we noted above, very few of these have been researched. (5) *Biological mechanisms underlying associations between psychological stress and URI should be investigated in viral exposure studies.* Control over extraneous factors (e.g., smoking, alcohol consumption, exercise) that may affect URI can be controlled or at least adequately assessed in such studies, which should aid in the detection of mechanisms. (6) *The results obtained from the experimental, viral inoculation studies should be used as sources of hypotheses that can be tested in real world settings.* Although experimental infection studies lend themselves to the investigation of psychobiological mechanisms involved in URI, it is critical to establish their relevance outside the laboratory. As with studies of cardiovascular reactivity, it is important to demonstrate the clinical significance of laboratory results. Field studies will also be necessary to determine the relative importance of psychobiological relations in comparison to other risk factors in the community. (7) *The impact of psychosocial interventions designed to capitalize on results obtained from the experimental, viral inoculation studies should be assessed in real world settings.* The effectiveness of psychosocial interventions in ameliorating a number of health problems (e.g., cardiovascular disease, cancer) is increasingly being investigated. If an appropriate psychosocial intervention were found to result in reduced stress and reduced URI, one could make a compelling case for causal relationships in a field study. Such intervention studies would also be informative with regard to the public health significance of psychosocial effects in URI.

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CONDITIONED EMOTIONAL DISTRESS AND INTRUSIVE THOUGHTS IN CANCER CHEMOTHERAPY PATIENTS,

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Empirical support for the view that conditioning processes play a key role in the development of core symptoms (e.g., intrusive thoughts) of posttraumatic stress disorder is scant. We examined relations between patients' intrusive thoughts about chemotherapy and conditioned emotional distress to clinic cues.

Women (N=37) with early stage breast cancer, who received 8 cycles of standard chemotherapy (Chemo), were assessed for intrusive thoughts (Impact of Events Scale) at their final infusion. Pre-chemo emotional distress was assessed in the clinic at each infusion, using a visual analog scale (0-100) and the Profile of Mood States (POMS). Post-chemo distress was assessed (0-100) by telephone interview. As in previous studies, conditioned distress was operationally defined as pre-chemo distress at infusions 2-7, controlling for distress at infusion 1.

Twenty-eight patients (76%) had intrusive thoughts about chemotherapy. Patients with intrusive thoughts had higher levels (p's<.02) of conditioned distress (VAS, POMS) but did not have higher levels of post-chemo distress.

These results are consistent with the view that conditioning mechanisms contribute to the development of intrusive thoughts in individuals confronting severe life stressors.

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STRESS, IMMUNE MODULATION, AND INFECTIOUS DISEASE DURING CHEMOTHERAPY FOR BREAST CANCER

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Patients receiving cytotoxic chemotherapy for cancer have an increased risk of infectious disease, which has previously been attributed solely to the immunosuppressive side-effects of chemotherapy (e.g., neutropenia). However, several lines of evidence suggests that psychological factors may also play a role: 1) In otherwise healthy individuals, emotional distress affect the incidence and severity of infectious disease. 2) Emotional distress is known to influence immune function in healthy individuals. 3) Cancer and its treatment are severe life stressors, which can result in psychological distress experienced on a daily basis with further increases on days of chemotherapy infusions. 4) After one or more pairings of clinic cues with infusions of immunosuppressive chemotherapy, some patients develop conditioned changes in immune defenses. Initial analyses have revealed an association between emotional distress and the absolute neutrophil count (a classic measure of immunologic recovery from chemotherapy). In addition, distress is associated with reduced levels of natural killer cell activity, which may have implications for defense against viral infection. Greater understanding of the processes involved in these interactions in cancer patients may lead to novel therapeutic approaches.

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SYM 26S* STRESS, PSYCHONEUROIMMUNOLOGY, AND CANCER

CHAIR: Andrew Baum, Ph.D., University of Pittsburgh Cancer Institute **PARTICIPANTS:** Michael Antoni, Ph.D., University of Miami, Dana Bovbjerg, Ph.D., Memorial Sloan-Kettering Cancer Center, Barbara Andersen, Ph.D., Ohio State University and Gieta van der Pompe, Ph.D., Helen Dowling Institute, The Netherlands

Advances in the study of stress, its effects on cancer and immunity, and on the links between immune system functioning and cancer etiology and progression have led to systematic investigation of immune status as a mediator of increasingly clear stress effects on cancer. Research has established clear relationships between stress and a number of indicators of immune function, including natural killer cells (NK), thought to be integral in cancer defense. This symposium will consider studies of stress and cancer course focusing on immune status as a mediator of these stress effects. Presentations will address the role of stress and immunity in production of cervical intraepithelial neoplasia, infectious illness and chemotherapy, progression of breast cancer and the impact of adrenergic challenge on immune status among breast cancer patients and healthy controls.

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C104 CONTROL ATTRIBUTIONS PREDICT PRE-CHEMOTHERAPY INFUSION DISTRESS

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A sense of control is a major predictor of an individual's response to a stressor. However, the construct of control has received little attention in individuals facing cancer-related stressors. The present study examined the possibility that generalized propensities for attributions of control, as well as patients' beliefs about their ability to control specific aversive side effects of chemotherapy might predict levels of emotional distress at treatment infusions.

Twenty three women (mean age=48; 91% white) with Stage I or II breast cancer were recruited prior to adjuvant outpatient chemotherapy. External, internal, and chance attributions of control were assessed with the Multidimensional Health Locus of Control (MHLC) scale. Patients' levels of perceived control over 25 chemotherapy side effects were assessed with a Symptom Control Scale (SCS), given prior to the first treatment infusion. Distress was assessed with the Profile of Mood States (short version) before Infusions 1 and 2.

Confirming previous reports, patients' distress levels were significantly ($p < .05$) higher at Infusion-1. Higher levels of distress at Infusion-1 were predicted by lower scores on the internal control subscale of the MHCL and by higher scores on the chance subscale, but not by scores on the SCS. Higher levels of distress at Infusion-2 were not predicted by scores on the MHCL, but were predicted by higher scores on the SCS.

The results suggest that a general propensity to believe in greater personal control is associated with reduced apprehension about beginning chemotherapy treatment (a potent medical stressor). After experiencing chemotherapy, however, patients' specific perceptions of their ability to control chemotherapy side effects become more predictive of distress. Greater initial confidence in one's ability to control treatment side effects appears to be a risk factor for distress prior to subsequent treatment infusions.

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APPENDIX II

STUDY MEASURES

INSTRUCTIONS: Listed below are illnesses that you may have experienced since your last chemotherapy treatment. If you had the illness since your last chemotherapy infusion, make an "**X**" in the box marked "**YES**" and let us know if you had this type of illness more than once. Then indicate as best you can, how many days in total you were sick with each type of illness. If you **DID NOT HAVE** the illness, make an "**X**" in the box marked "**NO**".

SINCE YOUR LAST TREATMENT, Did you have any of the following illnesses?	YES	NO	**IF YES,** How many separate times? (circle)				**IF YES,** How many days in total were you sick? (circle)			
Cold (runny nose, stuffy nose, sore throat, cough, etc.)			1	2	3	4+	1-3	4-7	8-14	15-21
Sinus infection (pain radiating from sinuses, headache)			1	2	3	4+	1-3	4-7	8-14	15-21
Flu (fever, chills, headache, muscle aches, etc.)			1	2	3	4+	1-3	4-7	8-14	15-21
GI virus (diarrhea, nausea/vomiting, etc.)			1	2	3	4+	1-3	4-7	8-14	15-21
Mouth/lip sores (blisters, lesions, etc.)			1	2	3	4+	1-3	4-7	8-14	15-21
Urinary infection (cloudy urine, burning sensation, urgency, etc.)			1	2	3	4+	1-3	4-7	8-14	15-21
Skin infection (redness, heat, swelling, etc.)			1	2	3	4+	1-3	4-7	8-14	15-21
Vaginal infection (itching, discharge, etc.)			1	2	3	4+	1-3	4-7	8-14	15-21
Other illness? What? ☛_____			1	2	3	4+	1-3	4-7	8-14	15-21
Other illness? What? ☛_____			1	2	3	4+	1-3	4-7	8-14	15-21

Did any of the illnesses listed above cause you to miss any days from work since your last chemotherapy treatment? (If you are not currently working, did any of these illnesses cause you to reduce your activities)?

____ Yes ____ No If yes, how many days in total ____?

Daily Assessment (last 24 hrs): Please fill this out at bedtime. Please put the thermometer under your tongue now.

ID_____ Date of the Day you are rating_____ Current Time _____ (circle) am pm
Day (circle): Su M T W Th F S Is this being completed for:(circle) Today or Yesterday?

Please indicate how you feel your life has been affected by the state of your health today, using a scale of **0** to **100**, where **0** means your life is normal with no changes because of the state of your health and 100 means your life is extremely unpleasant because of the state of your health _____

Please use the following words to describe your feelings for the entire day. Put a check in the circle under the phrase that best describes your mood:

	Does not apply	Slightly applies	Definitely applies		Does not apply	Slightly applies	Definitely applies
Angry	( )	( )	( )	Elated	( )	( )	( )
Sad	( )	( )	( )	Tired	( )	( )	( )
Clutched up	( )	( )	( )	Kindly	( )	( )	( )
Concentrating	( )	( )	( )	Skeptical	( )	( )	( )
Playful	( )	( )	( )	Self-centered	( )	( )	( )
Energetic	( )	( )	( )	Leisurely	( )	( )	( )

How emotionally upset have you been today? On a scale of 0 (not at all) to 100 (as upset as I could be) _____.
How fatigued have you been today? On a scale of 0 (not at all) to 100 (as fatigued as I could be) _____.
How nauseated have you been today? On a scale of 0 (not at all) to 100 (as nauseated as I could be) _____.
Did you have thoughts about chemotherapy today when you didn't mean to? (circle) YES NO

Please **CIRCLE** any of the following that you experienced today:

Pain	Feeling sick (malaise)	Difficulty concentrating	Change in appetite	Post nasal drip	Problems with urination	Change in menstrual flow
Feverish	Fatigue	Dizzy spells	Sore throat	Mouth sores	Heartburn	Vaginal discharge
Chills	A cold	Allergies	Hoarse	Joint pain	Constipation	Skin rash
Hot Flashes	Drowsiness	Runny Nose	Cough	Nausea	Diarrhea	Dry heaves
Night Sweats	Headache	Stuffy nose	Phlegm	Vomiting	Numbness	Muscle weakness
Too little saliva	Sneezing	Flu	Cold sore	Sinus infection		

Did any of the above cause you to cut down your activities today? (circle) YES NO

Was anyone who lives or works closely with you sick today? (circle) YES NO

Who?_____ What kind of illness?_____

How much sleep did you get last night? _____hrs _____mins; Did you have trouble getting to sleep? (circle) YES NO

Did you have trouble staying asleep? (circle) YES NO Did you get as much sleep as you wanted? (circle) YES NO

On a scale of 0 (worst possible) to 100 (best possible) how well did you sleep? ____

How many times did you awaken during the night? _____; Why?_____

How long was your longest awakening? _____hrs _____mins

Did you take any naps today? (circle) YES NO; If yes, for how long? _____hrs _____mins

How many cigarettes did you smoke today?_____ How many alcoholic drinks did you consume today?_____

How many caffeinated beverages (e.g., cans of cola, cups of coffee) did you drink today? _____

Did you take <u>any</u> drugs/medicine today? YES NO → What? _____

Did you cry today? (circle) YES NO _____

Did you laugh today? (circle) YES NO _____

Did you exercise today? (circle) YES NO _____

_____

What is your temperature? ___ ___ • ___ degrees

1. Here is a list of troublesome things that sometimes happen to people. Please check the line by each one that happened to you during the past 24 hours.

_____ A lot of work at home

_____ A lot of work at job or school

_____ A lot of demands made by your family

_____ A lot of demands made by other relatives or friends

_____ Spouse/Partner sick or injured

_____ Your child sick or injured

_____ Other relative sick or injured

_____ Injury to yourself

_____ A financial problem

_____ Spouse/Partner ignored you

_____ Witnessed something unusual (hold-up, etc.)

_____ Death of a relative

_____ Problem with transportation

_____ Other personal problems

What? _____

_____

_____

_____

_____

2. We would like to know about any tension or argument you had with any of these people during the past 24 hours. Please check each box that applies.

_____ Your spouse/partner

_____ Your child(ren)

_____ Parent

_____ Parent-in-law

_____ Brother or Sister

_____ Other relative

_____ Friend

_____ Neighbor

_____ Subordinate at work

_____ Coworkers

_____ Supervisor at work

_____ Someone else

3. Here is a list of pleasant things that sometimes happen to people. Please check the line by each one that happened to you during the past 24 hours.

_____ Positive interactions at work

_____ Socializing with staff, coworkers, etc.

_____ Physical activity done alone (working out)

_____ Vacation or day off spent at home

_____ Close interaction with spouse/partner

_____ Sexual interaction with spouse/partner

_____ Receiving from or giving praise to spouse/partner

_____ Child(ren) getting along well together

_____ Close interactions with child(ren)

_____ Other pleasant experiences:

What? _____

_____

_____

_____

_____