Psychological Stress and Susceptibility to Upper Respiratory Infections

SHELDON COHEN

Department of Psychology, Carnegie Mellon University, Pittsburgh, Pennsylvania

The biologic plausibility of a link between psychological states and host resistance is discussed. Although there is substantial evidence for the association between psychological stress and both cellular and humoral immune response, these data do not necessarily suggest increased susceptibility to infectious agents among stressed persons. Epidemiologic and viral-challenge studies suggest that psychological stress is a risk factor for upper respiratory infections with the strongest evidence provided by recent well-controlled, prospective viral-challenge trials. However, there is still little direct evidence for the nature of neuroendocrine, immune, or behavioral pathways through which stress might alter susceptibility. Cohen S. Psychological stress and susceptibility to upper respiratory infections.

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Over the last 15 yr considerable evidence has accumulated suggesting that psychological stress influences susceptibility to and progression of upper respiratory infections in humans. We now have biologically plausible explanations for stressor influences on the pathogenesis of infectious agents, substantial evidence that stressors can alter both cellular and humoral immune function, and evidence for an association between stress and host resistance to a number of upper respiratory viruses.

PLAUSIBLE EXPLANATIONS FOR STRESSOR INFLUENCES ON PATHOGENESIS OF UPPER RESPIRATORY INFECTIONS

Given exposure to an infectious agent, susceptibility to infection is presumed to be primarily mediated by immune function. There is substantial evidence that psychological stress and other psychosocial factors influence immunity (1–3) as well as basic research delineating the pathways through which this influence may occur. Stress may influence immunity through direct innervation of the central nervous (CNS) and immune systems or through neuroendocrine-immune pathways. Direct neural pathways linking the CNS to the immune system have been identified (4, 5). In the case of hormonal pathways, catecholamines secreted by the adrenal-medulla in response to stressors and stressor-triggered pituitary-mediated hormones such as cortisol and prolactin have been associated with modulation of immune function (6–8). Moreover, receptors for ACTH, TSH, growth hormone, prolactin, and catecholamines have been found on lymphocytes (8). The existence of these receptors suggests that these hormones play a role in modulating lymphocyte function.

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Correspondence and requests for reprints should be addressed to Sheldon Cohen, Ph.D., Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213.

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Behavioral changes that occur as adaptations or coping responses to stressors may also influence immunity. For example, persons exposed to stressors often engage in poor *health practices*, such as smoking, poor diets, and poor sleeping habits (9, 10) that may have immunosuppressive effects (11, 12). Stressors can also influence susceptibility to infection by influencing whether and for how long persons are exposed to infectious agents. For example, stressed persons often engage in social coping, i.e., drawing on resources from their social networks (13). Increased interaction with others results in greater risk of exposure to infectious agents and consequent infection. Other stressor-elicited behaviors, such as poor hygienic practices, could also increase exposure.

EVIDENCE FOR STRESSOR ALTERATION OF IMMUNE FUNCTION

Both human and infrahuman studies indicate that various stressors modulate both cellular and humoral measures of immune function (1, 14). This includes human research on immunomodulating effects of *acute* stressors, such as psychological challenges in the laboratory (15, 16), as well as *chronic* stressors, such as living near a nuclear power plant (17), separation and divorce (18, 19), caregiving for Alzheimer patients (19), and bereavement (20, 21).

Although the effects of stressors on immune response are often described as immunosuppressive, the implications of stressor-induced immune changes for disease susceptibility are not clear (1, 22). First, in studies of stressor effects on immunity, the immune responses of stressed persons typically fall within normal ranges (8, 23). Second, we know very little about variations in the immune status in healthy persons as a predictor of disease susceptibility. Finally, the immune system is complex. One or even several measures of immune function may not provide an adequate representation of host resistance.

The first two comments apply primarily to the risk for infection among healthy individuals. However, stress and other psychosocial factors may have their greatest effect among those whose immune systems are already compromised, such as the elderly, individuals whose health is already impaired, and patients with immunosuppressive disease (24).

STRESSORS AND SUSCEPTIBILITY TO INFECTIOUS DISEASE

Stressful life events are commonly believed to suppress host resistance to infection. When demands imposed by events exceed a person's ability to cope, a psychological stress response composed of negative cognitive and emotional states is elicited. It is these responses that are thought to influence immune function through their effects on behavioral coping and neuroendocrine response. In this section, we review the role of stressful life events and consequent cognitive and emotional states in host resistance to upper respiratory infections. Stressful events are typically measured by scales that cumulate the number of major or minor (daily) events that have occurred in the near past. Examples of major life events include divorce and death of close family members and friends. Minor (daily) events include losing keys and having arguments. Measures of cognitive responses typically include feelings (perceptions) of stress or distress, and emotional measures include responses such as anxiety, fear, depression, and anger. Stressful life events and cognitive and emotional response measures are used individually and together to assess psychological stress in this literature.

The following discussion is limited to studies that employ standardized measurement, include control groups, and use procedures allowing statistical inference. It is also limited to studies in which clinical illness is diagnosed by a physician using a standard protocol, or illness is verified through biological means, e.g., viral shedding or increases in pathogen-specific antibody. We focused on studies of verified illness because those using self-reports of symptoms or illnesses without verification may reflect psychosocial influences on illness cognition (perception and reporting) rather than underlying pathology (25). We will review the retrospective and then prospective epidemiology and discuss the early viral-challenge trials. Finally, our viral-challenge work and a replication of that work by another laboratory are summarized.

Retrospective Studies

In a study by Jacobs and colleagues (26), university students completed both stressful life event and psychological distress scales. More physician-diagnosed cases of upper respiratory infections (URI) were found among those with relatively numerous life changes. The effect occurred only for "personal failure and role crisis" events. URI incidence was also associated with greater defiance, danger-seeking behavior, and unpleasant emotional states. In another student sample, Alexander and Summerskill (27) found no differences between stressful (e.g., exam and pre-exam) and nonstressful periods on campus and diagnosed incidence of URI. Nor were academic probation, university disciplinary action, or university activities related to URI incidence. However, persons seeking help at the mental health clinic had a higher incidence of URI than the sample as a whole. Finally, in a community study of children (mean age 4.3 yr), Boyce and coworkers (28) found that increased life events (as retrospectively reported by parents) were associated with increased duration of illness and illness severity (as evaluated by health professionals) but not with number of illnesses.

Prospective Studies

In the retrospective literature reviewed in the previous section, stress and illness were measured concurrently or stress was assessed retrospectively. Hence, associations between psychological stress and disease reported in these studies might be attributable to illness causing stress. In the following studies, stress measures were taken in healthy subjects who were subsequently monitored for disease onset. By measuring stress *before the onset of the disease*, it is possible to eliminate a disease-resulted-in-stress interpretation of reported associations.

In an early study, Meyer and Haggerty (29) followed 100 members of 16 families for a 12-mo period. Family diaries were used to record stressful life events. Throat cultures (screened for streptococcal infections) were made every 3 wk and at times of acute illness. Blood (for antibody levels) was drawn every 4 mo. Daily life events that disrupted family and personal life were four times more likely to precede than to follow new streptococcal and nonstreptococcal infections and associated symptoms. In addition, chronic family stress (as judged by observers) was related to greater numbers of new infections, prolonged production of the bacterium without symptoms, higher streptococcal illness rates, and elevated antibodies to a streptococcal-produced toxin (antistreptolysin O). Separate analyses indicated that a large group of control variables, including sex, family history of respiratory infections, family size, and allergic history, were unrelated to infectious outcomes.

Similar results were reported in a study of viral URIs in 235 members of 94 families (30). Diary data on respiratory symptoms were collected daily for 6 mo. Major stressful life events were assessed before and after the study period, and daily life events and psychological distress were assessed at study onset and twice during the study. Illness episodes were validated by viral cultures of nose and throat swabs, and analyses included controls for a wide range of other factors, such as sex, age, family size, and proneness to infection. High stress was defined as above median scores on all three stress measures: life events, daily events, and psychological distress. Those reporting higher levels of stress over the course of the study (retrospective analysis) experienced more verified episodes and more symptom days of respiratory illness. Those with higher levels of stress at the beginning of the study (prospective analysis) demonstrated similar but somewhat attenuated effects of stress on number of episodes and days with symptoms. In analyses designed to determine independent effects of the three stress measures, pre-study daily event frequency was positively associated with verified episodes, and pre-study major stressful life events were positively associated with the number of symptom days in verified episodes.

Two prospective studies have addressed psychological susceptibility to influenza. In the first study (31), 480 male employees of a military research installation completed a series of psychological distress scales 6 mo before an epidemic of Asian influenza. Based on test scores, they were classified as either high or low stress. During the subsequent epidemic period, all persons presenting an influenza-like illness were followed over a 3-wk period to evaluate acute disease. Infection was verified both through antibody increase and virus isolation. Illness reports in the high stress group were about three times higher than in the low stress group. However, there were no differences in infection rates or illness severity.

In the second flu study (32), 246 individuals in 58 families completed instruments assessing family relationships and individual stressful life events before the start of flu season. Antibodies to two strains of influenza B were measured before and after flu season. Incidence of illness was defined as a fever greater than 100° F, a criterion number of flu symptoms, and "influenza infection" (isolation of flu virus in throat culture or a fourfold increase in antibodies to influenza B). They found that incidence of disease was greater in stressed ("rigid" and "chaotic") families than in nonstressed ("balanced") families. Incidence also increased as family cohesiveness increased, possibly because increased social contacts among family members result in increased exposure (33). Illness incidence was not related to life events or family satisfaction.

In summary, evidence from epidemiologic studies verifying infectious episodes suggests that stress increases risk for upper respiratory disease. The retrospective work is fairly consistent in this regard, but the prospective studies are mixed. Two com-

munity-based studies of families (29, 30) found support for reliable increases in verified disease with increased life events, although a third (32) did not. Two of these studies (29, 32) similarly indicated evidence for greater incidence of disease among those with relatively high levels of family distress. Finally, Cluff and colleagues (31) found that psychological distress was related to illness reporting but not to verified illness.

Prospective Viral-Challenge Studies

Several studies have exposed healthy volunteers to specific viruses in attempts to determine whether psychological factors (measured before the viral challenge) influence susceptibility to URI. Advantages of this paradigm include eliminating the possible role of psychological effects on exposure, controlling dosage of the infectious agent, and allowing biologic verification through tests for the specific virus used.

Three of the early viral-challenge studies examined the role of stress in susceptibility to infection. In the first study (34), 52 healthy volunteers completed an interview on stressful life events. Subsequently, they were inoculated with two rhinoviruses (RV2 and RV31) and followed daily (in isolation) for 1 wk. After controlling for pre-challenge antibodies to the two rhinoviruses, total amount of virus shedding (extent of infection) was predicted by only one of five life event scores: increased shedding (but not a combined measure of signs and URI symptoms) was associated with increases in total level of purposeful activity and social contact. None of the other stressor measures (including the more standard index of life events) was related to viral shedding or symptom scores.

In the second study, Broadbent and colleagues (35) report data from 39 persons receiving rhinoviruses (RV9 or RV9 + RV14) and 51 receiving influenza viruses (A Munich or A California). Total clinical symptom score (combining both signs and symptoms) was predicted by a personality measure, obsessionality, and by total psychological distress. In the influenza trials, the total clinical symptom score was similarly predicted by greater obsessionality. However, infection (viral isolation) was not predicted by any of the psychological measures.

In the third study, Greene and coworkers (36) examined effects of self-reported life events and moods in 33 subjects receiving nasal inoculations of an influenza virus (A Victoria) and the drug isoprinosine. Life events and mood states were assessed on day 1; symptoms were rated on day 1 and twice daily for the remainder of the week. On the second day, subjects received nasal inoculation of the virus. Neither life events nor moods were related to antibody production, viral isolation, or symptoms. Similar results were found in a study with a larger sample. Locke and Heisel (37) gave 124 volunteers a swine (A/NJ/76) flu vaccine and had them complete life events and mood scales. Again, no relationship was found between the psychological measures and production of specific antibodies.

In summary, early viral-challenge studies provide mixed evidence for a relationship between stress and susceptibility to rhinovirus infections and no evidence for a relationship between stress and influenza. In light of support for a relationship between stress and URI in epidemiologic field data, the failure of viral-challenge studies to find a consistent relationship between stress and susceptibility to URI is surprising. It may be that field results are attributable to stress-induced social contacts, resulting in increased exposure to infectious agents and hence, because viral-challenge studies control for exposure, they do not find such results. However, methodologic limitations of the early challenge studies may also account for their failure in this regard. Individual studies suffer from insufficient sample sizes, concurrent administration of drugs, lack of information on overall rates of infection in response to the dose of virus administered, and controls for important predictors of susceptibility, such as pre-existing antibodies to the infectious agent, gender, age, and number of previous infections (38).

THE COMMON COLD STUDIES

In our study, we pursued whether stress places people at greater risk for infectious disease and at the same time attempted to identify the behavioral and biological pathways through which such relations operate. For stressful events to influence susceptibility, they are presumed to be appraised as stressful (as exceeding ability to cope) and to consequently elicit an emotional response. This emotional response is thought to trigger either behavioral (e.g., increased smoking) or neuroendocrine (e.g., increases in circulating epinephrine, norepinephrine, or cortisol) responses thought to influence the immune system's ability to respond to a challenge. The first study was designed to examine the psychological, behavioral, and biological pathways thought to link stressful events to illness susceptibility, while carefully controlling for a variety of other factors that might influence risk for infectious disease. The second study is a replication of this work conducted by an independent laboratory. Finally, we summarize a recently completed study examining the role of psychological stress in the severity of disease among clinically ill volunteers.

British Cold Study

The data described here are from a trial conducted at the Medical Research Council's Common Cold Unit in the United Kingdom between 1986 and 1989 (39, 40). In this study, we assessed stressful life events, perceived stress, and negative emotions *before* experimentally exposing subjects to a common cold virus or saline. We then carefully monitored subjects for the development of infection and clinical illness. By intentionally exposing people to an upper respiratory virus, we were able to control the possible effects of stressful events on exposure to infectious agents (as opposed to their effects on host resistance). In the following section, we examine the relationship between each of the three stress scales and risk for ways through which each might influence susceptibility to infectious disease and discuss differences in relationships between individual scales and illness susceptibility in terms of the components of psychological stress that each of the scales assess.

Methods. The subjects were 154 men and 266 women volunteers 18 to 54 yr old. All reported no chronic or acute illness or regular medication regimen and were judged in good health after examination. During their first 2 d in the clinical unit, they were given a thorough medical examination, completed psychological stress, personality, and health practice questionnaires, and had blood drawn for immune and cotinine (a metabolite of nicotine) assessments. Subsequently, volunteers were exposed via nasal drops to a low infectious dose of one of five respiratory viruses: rhinovirus types 2 (n = 86), 9 (n = 122), and 14 (n = 92), respiratory syncytial virus (n = 40), and coronavirus type 229E (n = 54). An additional 26 volunteers received saline. For 2 d before and 7 d after viral challenge, volunteers were quarantined in large apartments (alone or with one or two others). Starting 2 d before viral challenge and continuing through 6 d postchallenge, each volunteer was examined daily by a clinician using a standard respiratory sign-symptom protocol. Examples of items on the protocol include sneezing, watering of eyes, nasal stuffiness, sore throat, hoarseness, and cough. The protocol also included an objective count of the number of tissues used daily by a volunteer and body temperature (oral) assessed twice each day. Samples of nasal secretions were also collected daily to assess whether volunteers were infected by the experimental virus. Approximately 28 d after challenge, a second serum sample was collected to as-

sess changes in viral-specific antibody. All investigators were blind to volunteers' psychological status and to whether they received virus or saline.

Infection was detected directly by culturing nasal secretion samples (viral isolation) or indirectly through establishing significant increases in viral-specific antibody. A volunteer was deemed infected if virus was isolated in nasal secretion after viral challenge or there was a fourfold rise in pre- to post-challenge viral-specific serum antibody. Eighty-two percent (325) of the volunteers receiving virus were infected.

The criteria for clinical illness were both infection and a positive clinical diagnosis. At the end of the trial, the clinician judged the severity of each volunteer's cold on a scale ranging from nil (0) to severe (4). Ratings of mild cold (2) or greater were considered positive clinical diagnoses. Thirty-eight percent (148) developed clinical colds. None of the 26 saline controls developed colds. The subjects also rated the severity of their colds on the same scale. The clinical diagnosis was in agreement with the subject's rating in 94% of the cases.

We noted earlier that when demands imposed by events exceed ability to cope, a psychological stress response is elicited and that this response is composed of negative cognitive and emotional states. To assess the various components of this process, three kinds of measures of psychological stress were used: (*1*) number of major stressful life events judged by the respondent as having a negative impact; (*2*) perception that current demands exceed capabilities to cope; and (*3*) current negative emotions. The major stressful life events scale consisted of events that might happen in the life of the respondent (41 items) or significant others (26 items). The scale score was the number of negative events reported as occurring during the last year. The Perceived Stress Scale was used to assess the degree to which situations in life are perceived as stressful. Items in the scale were designed to tap how unpredictable, uncontrollable, and overloading respondents find their lives. Finally, the negative emotions scale included 15 items from Zevon and Tellegen's list of negative emotions. Data are also presented based on analyses using a psychological stress index created by quartiling each scale and summing quartile ranks for each subject.

Each analysis controlled (covaried) for the possible effects of a series of variables that might provide alternative explanations for a relation between stress and illness. These included prechallenge serostatus for the experimental virus, age, gender, education, allergic status, weight, season, number of others the volunteer was housed with, whether an apartment mate was infected, and challenge virus. Separate analyses were also conducted to assess the roles of health practices as possible pathways linking stress and susceptibility. Measures included smoking (serum cotinine), drinking alcohol, exercise, quality of sleep, and diet.

Because psychological stress could reflect stable personality styles rather than responses to environmental stressors, self-esteem and personal control (two personality characteristics closely associated with stress) were assessed before viral challenge. A third personality characteristic, introversion-extraversion, was also assessed.

Results. Highly stressed persons had higher rates of clinical colds irrespective of the stress scale. These effects were not attributable to the relationship between stress and health practices (smoking rate, drinking rate, diet, exercise, and sleep quality) or the personality characteristics. In a second series of analyses, we found the relationship between life events and colds was independent of the relationship between both perceived stress and clinical illness and negative emotions and clinical illness (40).

As interesting as the similar relationship between each stress scale and clinical illness is that these relations were not all mediated by the same biologic process. Negative life events were associated with greater rates of clinical illness, and this association was primarily mediated by increased symptoms among infected persons. Perceived stress and negative emotions were also related to clinical illness, but their associations with increased risk were primarily attributable to increased infection. These differences suggest that (a) the negative life events instrument measures something different than perceived stress and negative emotions scales, and (b) that the constructs they tap have somewhat different consequences for the pathogenesis of infectious illness.

The results presented so far have collapsed across viruses. When we examined each virus separately, we found a dose-response relationship between psychological stress (the stress index combining the three scales) and clinical illness in all five of the viruses (39). The consistency of the stress-illness relationship among three very different viruses—rhinovirus, coronavirus, and respiratory syncytial virus (as well as among rhinovirus types)—was impressive. This observation suggests that stress is associated with the suppression of a general resistance process in the host, leaving persons susceptible to multiple infectious agents (or at least agents attacking the upper respiratory tract), or that stress is associated with the suppression of many different immune processes, with similar results.

University of Virginia Cold Study

A subsequent study conducted at the University of Virginia also used life events, perceived stress, and negative emotion scales in predicting the incidence of clinical colds (41). The three scales were administered to the volunteers before being challenged with a rhinovirus (Hanks virus). Only volunteers who subsequently became infected were included in their analyses. Like the British study, those with more life events were more likely to develop clinical colds. However, perceived stress and negative emotions were unrelated to illness. Their failure to find associations of perceived stress and negative emotions with illness is *not* inconsistent with the results of the British work. This is because the design of the University of Virginia study included only infected persons, and hence, they could not assess susceptibility to infection. In the British study, perceived stress and negative emotions were associated with the incidence of clinical illness because they increased incidence of infections. Hopefully, future research will identify the components of psychological stress that are responsible for differential effects on pathology. However, a more important conclusion of these studies is that all of these instruments indicate what up to now has been somewhat speculative, that psychological stress is associated with increased susceptibility to biologically verified infectious disease processes.

Pittsburgh Cold Study

In a recent study, we addressed whether psychological stress (specifically negative emotions) alters the severity of clinical upper respiratory illness (42). Volunteers completed a questionnaire that assessed the extent to which they were experiencing negative moods, had blood drawn for specific antibody assessments, and reported baseline upper respiratory symptoms. Subsequently, the participants were given nasal drops containing an infectious dose of one of two respiratory viruses, Kawasaki A influenza virus (n = 33) or rhinovirus 39 (n = 53). After viral exposure, participants were quarantined in a hotel and monitored daily for signs and symptoms of upper respiratory infection and objective indicators of pathophysiology. Measures collected daily during the trial included samples of nasal secretions for detection of infection, facial tissues for assessing mucus secretion weights, and daily self-reports of negative emotional states and upper respiratory symptoms. Approximately 4 wk after participants were exposed to the virus, a second blood sample was collected from

each participant and analyzed for a second marker of infection: a fourfold increase over baseline in virus-specific serum antibody levels. The study focused on the number of symptoms reported by participants who developed biologically verifiable clinical upper respiratory illness.

As in the early study, clinical upper respiratory illness was defined as the combination of verified infection and symptoms. Those with verified infection were diagnosed as having a clinical illness if, after viral exposure, they either reported having a cold or flu or reported two or more upper respiratory symptoms not reported at baseline (70 participants). Analyses using a less stringent criterion for illness, infection alone (75 participants), supported identical conclusions.

The results were identical for the influenza and rhinovirus, and hence we report only the combined data here. Persons who reported more negative emotions at baseline were no different than their less emotional counterparts in regard to upper respiratory symptoms and mucus weights collected *before* viral challenge. However, negative emotions did predict symptoms and mucus weight *during illness*. Those volunteers reporting more negative emotions before being exposed to the virus reported more upper respiratory symptoms and had greater mucus weights during illness than the less emotional volunteers. The correlation between negative emotions at baseline and symptoms after viral exposure was 0.33 ($p < 0.01$) and between negative emotions and mucus weights after exposure was 0.26 ($p < 0.05$). In summary, negative emotions predict severity of illness as well as susceptibility.

CONCLUSIONS

There is substantial evidence for the plausibility of psychosocial influences on infectious upper respiratory disease in humans as well as evidence for a role of psychologic stress in determining susceptibility for a small number of infectious agents. However, we still know little about the nature of behavioral, endocrine, and immune changes that are responsible for psychosocial-induced changes in disease risk. Until there is more empirical evidence for specific mechanisms linking psychosocial factors to infectious disease, we will have little real understanding of the extent to which evidence deriving from current work generalizes to other disease models.

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