Psychological Stress, Immunity, and Upper Respiratory Infections

Sheldon Cohen[1]
Department of Psychology, Carnegie Mellon University, Pittsburgh, Pennsylvania

The belief that when we are under stress we are more susceptible to the common cold, influenza, and other infectious diseases is widely accepted in our culture. It is the topic of numerous contemporary newspaper and magazine articles and has even been addressed in the lyrics of a popular song ("Adelaide's Lament" from *Guys and Dolls*). The wide acceptance of this belief is also supported by data collected from participants in my studies. Sixty percent report that they are more likely to catch a cold during stressful than nonstressful periods of their lives. In this article, I review the scientific evidence that addresses this belief. How could psychological stress influence susceptibility to infectious disease? Is such a relation biologically and psychologically plausible? Is there convincing evidence that psychological stress influences susceptibility to upper respiratory infections?

HOW COULD STRESS INFLUENCE SUSCEPTIBILITY TO INFECTIOUS DISEASE?

Although constantly exposed to bacteria, viruses, fungi, and parasites that can cause infectious disease, we only periodically develop infectious illnesses. This is because our immune system protects us from infectious microorganisms. This defensive function is performed by the white blood cells and a number of accessory cells, which are distributed throughout the organs of the body. Stress is thought to influence susceptibility to infectious disease by compromising the effectiveness of the immune system. Persons with suppressed immune function are less able to fight off infectious agents and hence, given exposure to an agent, more likely to develop an infectious disease.

A simplified view of how stressful events in our lives might alter immunity is presented in Figure 1. When our demands are perceived to exceed our ability to cope, we label ourselves as stressed and experience a negative emotional response (Lazarus & Folkman, 1984). In turn, negative emotional responses could alter immune function through three different pathways (Rabin, Cohen, Ganguli, Lyle, & Cunnick, 1989). Nerve fibers connecting the central nervous system and immune tissue provide one path by which emotional responses may influence immunity. These nerves terminate in immune tissue, where they release chemicals that are thought to suppress the function of immune cells. Stress-induced emotions may also act through their influence on the central nervous system's production and release of hormones such as epinephrine and cortisol. These hormones circulate in the blood and can attach to receptors on immune cells, resulting in the cells' protective functions "turning off." The third mechanism by which stress may affect health derives from the role of behavioral patterns that reflect attempts to cope with negative emotional responses. For example, persons experiencing psychological stress often engage in unhealthy practices such as smoking and not eating or sleeping properly, and such behavioral changes may suppress the activity of the immune system. They may affect immune responses directly or may influence immune function by altering hormonal responses.

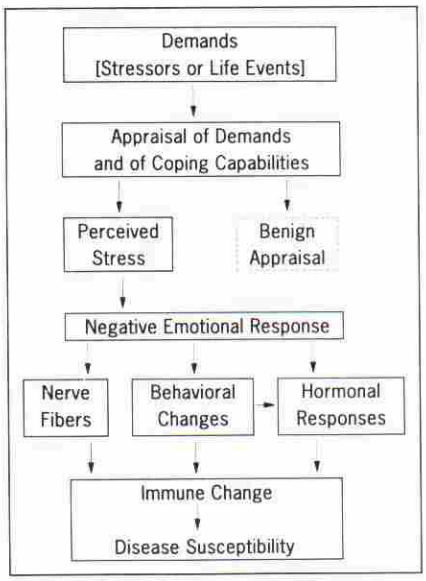

Fig. 1. Pathways through which stressful life events might influence the onset and progression of infectious disease. For simplicity, arrows are drawn in only one direction, from psychological characteristics to disease. This convention does not imply any assumptions about the existence of alternative paths.

DOES STRESS INFLUENCE IMMUNE FUNCTION?

As just discussed, the key link between psychological stress and susceptibility to infectious agents is thought to be the immune system. There is substantial evidence supporting the role of stress in the regulation of the human immune system. Suppression of immune function has been found among persons taking important exami-

nations (e.g., Kiecolt-Glaser et al., 1984); caring for relatives with chronic diseases (Kiecolt-Glaser, Glaser, et al., 1987); living near the site of a serious nuclear-power-plant accident (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989); suffering marital conflict (Kiecolt-Glaser, Fisher, et al., 1987); and reporting relatively high levels of unpleasant daily events (Stone et al., 1994), negative moods (Stone, Cox, Valdimarsdottir, Jandorf, & Neale, 1987), or perceived stress (e.g., Jabaaji et al., 1993). Suppression of immune function (called *immunosuppression*) has also been found in response to acute laboratory stressors, including working on challenging cognitive tasks, such as mental arithmetic, and delivering public speeches (e.g., Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991). Clinical depression has also been associated with decreased immune response (Herbert & Cohen, 1993).

DOES STRESS INFLUENCE SUSCEPTIBILITY TO UPPER RESPIRATORY INFECTIONS?

Do studies that demonstrate induced immunosuppression under stressful conditions provide compelling evidence for stress-induced susceptibility to infectious disease? In general, these data are thought to be consistent with, but not definitively supportive of, the hypothesis that stress results in increased susceptibility to disease. The immune response involves a complex cascading series of events. Because studies of stress and immunity are limited to assessing very few markers of immune function in a limited time span, they can provide only a very rough estimate of the body's ability to mount such a defense (Cohen & Williamson, 1991).

Naturalistic Studies of Stress and Upper Respiratory Infection

A more direct approach to addressing the role of psychological stress in susceptibility to infection is examining the correlation between stress and infectious disease in natural settings. Because upper respiratory infections are by far the most prevalent of infectious diseases, the common cold and influenza have been adopted as the primary models for studying how stress might influence susceptibility. A large group of studies has found correlations between psychological stress and self-reported colds and influenza (reviewed in Cohen & Williamson, 1991). This work, however, is generally difficult to interpret. In many cases, third factors such as social class, age, or ethnic background might be responsible directly for increases in both stress and disease. Moreover, because this work is primarily retrospective, being ill may have caused stress rather than vice versa. Another problem is that unverified self-reports of illness are difficult to interpret. Although they may indicate underlying disease pathology, they may also reflect stress-induced biases to view ambiguous physical sensations as symptoms, and to interpret symptoms as indicating the onset of disease (e.g., Cohen et al., 1995).

There are a few investigations that have associated psychological stress and biologically verified (as opposed to self-reported) upper respiratory disease (e.g., Graham, Douglas, & Ryan, 1986; Meyer & Haggerty, 1962). Verification was accomplished by establishing the presence of a responsible bacterium or virus in nasal secretion or of an elevated level of antibody to the infectious agent in blood (serum).[2] In these studies, measures of psychological stress were administered to healthy subjects who were subsequently monitored for up to 12 months for the development of upper respiratory infections. For those reporting infections, nasal secretions or blood samples were used to biologically verify the disease. These studies have found links between psychological stress and the subsequent development of colds and influenza. These results, however, may be attributable to stress-induced increases in exposure to infectious agents, rather than stress-induced immunosuppression. For example, persons under stress often seek out other people, consequently increasing the probability of exposure. The studies also fail to provide evidence about behavioral and biological mechanisms through which stress might influence a person's susceptibility to infection.

Viral-Challenge Studies

In my own work, I have adopted a procedure in which after completing stress questionnaires, volunteers are intentionally exposed to a common cold virus (in nasal drops) and then quarantined and monitored for 5 or more days for the development of disease.[3] Approximately one third of the volunteers exposed to a virus develop a biologically verified clinical cold. The viral-challenge procedure has a number of advantages over naturalistic studies. By experimentally exposing persons to a virus and limiting their contact with other people, I eliminate the possibility that the results are attributable to stress increasing social contact and hence exposure to infectious agents. Moreover, because participants are closely monitored after exposure, it is easier to verify disease onset and to assess the roles of behavioral and biological pathways that might link stress to disease

susceptibility. Finally, this methodology allows for a more refined assessment of the body's response to a virus. Specifically, after exposure to a virus, persons can become infected (i.e., their cells replicate the virus) without developing symptoms. In the viral-challenge trials, body fluids used to determine infection are drawn from subjects both with and without upper respiratory symptoms, allowing the identification of subclinical (i.e., with few if any symptoms) as well as clinical infections.

In an attempt to take advantage of the strengths of this methodology, my colleagues and I conducted a viral-challenge study addressing the role of stress in susceptibility to the common cold (Cohen, Tyrrell, & Smith, 1991, 1993). By using a prospective design in which psychological stress is assessed before participants are exposed to a virus, we were able to eliminate the possibility that illness causes stress as an interpretation of our results. Because the primary outcome in viral-challenge studies is categorical (sick or not), large sample sizes are required to maximize study sensitivity. Hence, we accumulated data from 420 healthy volunteers. Collection of these data required more than 40 separate 1-week trials conducted over 4 years. Our main hypothesis was that the higher the level of psychological stress, the higher the risk of developing the upper respiratory illness caused by the virus.

Each participant completed psychological stress questionnaires just prior to being exposed to one of five viruses known to cause common colds. A group of control participants received saline in nasal drops instead of a virus. After 7 days of quarantine, each participant was classified as not infected, infected but not ill, or infected and ill (clinical cold). As expected, none of the participants exposed to saline developed clinical colds, so this control group was not included in subsequent analyses.

The model in Figure 1 suggests that when demands imposed by events in someone's life exceed that person's ability to cope, he or she makes a stress appraisal (perceives stress), and in turn experiences a negative emotional response. In this work, we employed instruments to assess each phase of the stress response: a stressful-life-event scale to measure the cumulative event load, a perceived-stress scale to assess perceptions of overload-induced stress, and a measure of negative emotional response. Figure 2 presents the relations we found between stress (high or low, split at the median response) as assessed by each measure and the probability of developing a clinical cold. For all three stress measures, participants reporting high stress were more likely than those reporting low stress to develop a viral disease. These relations were found consistently for all five viruses. Moreover, these results could not be explained by stress-elicited differences in health practices, including smoking, alcohol consumption, exercise, eating, or sleeping habits. They also could not be explained by stress-induced changes in a series of relatively basic measures of immune status—the numbers of various white blood cell populations or total (nonspecific) antibody levels.[4] A large group of plausible alternative factors that might be correlated with both stress and disease (e.g., age, sex, education, and personality characteristics such as self-esteem and personal control) were also unable to account for the relation between stress and susceptibility. In sum, the results provided strong support for a relation between psychological stress and susceptibility to developing a clinical cold, but did not provide confirming evidence for either a biological or a behavioral pathway responsible for the association.

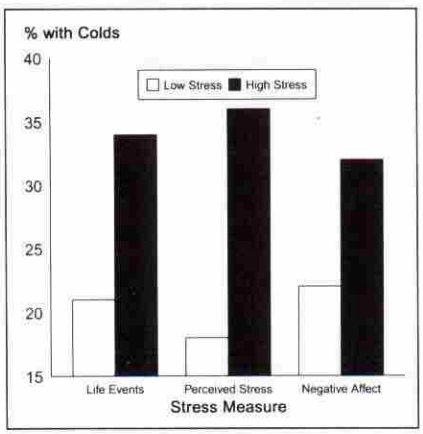

Fig. 2. Percentage of persons developing biologically verified clinical illness as a function of stressful life events, perceived stress, and negative affect. Each participant was exposed to one of five upper respiratory viruses. For each measure, scores were categorized as indicating high or low stress according to whether they were above or below the median score. Adapted from Cohen, Tyrrell, and Smith (1993), with permission of the American Psychological Association.

This study also addressed the validity of the hypothesis that stressful life events influence disease susceptibility by eliciting perceptions of stress and consequent negative emotional responses. However, the data did not totally support this perspective. First, the relation between stressful life events and risk of developing a cold was independent of the relations between perceived stress and colds and between negative affect and colds. That is, more stressful events were associated with greater susceptibility to disease irrespective of whether those events elicited perceptions of stress and negative affect. Second, the association of life events with illness was attributable to different biological processes than the associations of perceived stress and negative affect with illness. Increased risk for developing clinical colds could occur because stress increases the probability of the infec-

tious agent replicating (infection), or because stress increases the production of histamines, bradykinins, or other chemicals that trigger symptoms after infection. In this study, becoming biologically infected was associated with high levels of perceived stress and negative affect, but developing clinical symptoms after infection was associated with high numbers of stressful life events. The fact that these scales have independent relations with clinical illness and that these relations are mediated by different biological processes challenges the assumption that perceptions of stress and negative affect are necessary for stressful life events to influence disease risk. A subsequent viral-challenge study conducted in another laboratory also found that life events and increased susceptibility had a relation independent of perceived stress and negative affect (Stone et al., 1993). As in our data, higher numbers of stressful events were associated with increased symptoms after infection.

A plausible explanation for the direct association between stressful life events and susceptibility is that the effort of coping with events, whether or not successful, results in hormonal responses that modulate immunity (Cohen, Evans, Stokols, & Krantz, 1986). In short, self-perceived negative emotional response may not be the only psychological pathway able to trigger hormonal responses critical to influencing immune function and disease susceptibility.

In sum, there is substantial evidence that both stressful life events and psychological stress (perceptions and negative affect) influence susceptibility to upper respiratory infections. These effects are not a consequence of unhealthy behaviors elicited by stress. We also lack direct evidence that increased susceptibility is attributable to stress-induced immunosuppression. The immune system, however, is terribly complex, and the measures used in human studies may not adequately assess the components most relevant to resisting upper respiratory infections. Finally, contrary to accepted stress and coping theory, the relation between stressful events and susceptibility to infectious disease does not depend on elevated perceptions of stress and negative emotional response.

CONCLUSIONS

The literature linking stress, immunity, and upper respiratory infection is in many ways impressive. First, it provides psychologically and biologically plausible hypotheses for how psychological factors might influence immunity and infectious disease. Second, it provides substantial evidence that psychological factors can influence indicators of immune status and function. Third, it includes consistent and convincing evidence of links between stress and the onset of upper respiratory infections. Where it fails is in identifying the behavioral, hormonal, or immune system pathways that are responsible for the link between stress and disease susceptibility. Only by identifying these pathways will researchers be able to evaluate the extent to which work with upper respiratory viruses provides a generic model that will allow generalization to other infectious agents.

Acknowledgments—Preparation of this article was supported by a Research Scientist Development Award (K02MH00721) and by a grant (MH50429) from the National Institute of Mental Health. I am indebted to Mario Rodriguez and Roberta Klatzky for their helpful comments on an earlier draft.

Notes

1. Address correspondence to Sheldon Cohen, Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213.
2. Antibodies are protein molecules that attach themselves to invading microorganisms and mark them for destruction or prevent them from infecting cells. Each antibody recognizes only a single type of microorganism.
3. The diseases caused by these viruses are quite mild common colds. All study participants gave informed consent after receiving both oral and written descriptions of the diseases as well as all possible risks. Participants were examined at the end of the trial, and treatment was available for any complications.
4. A measure of total (nonspecific) antibody assesses the amount of antibody in circulation, but does not provide any information about the amount of antibody that is specific to, and therefore will fight off, a particular virus.

References

Cohen, S., Doyle, W.J., Skoner, D.P., Fireman, P., Gwaltney, J., & Newsom, J. (1995). State and trait negative affect as predictors of objective and subjective symptoms of respiratory viral infections. *Journal of Personality and Social Psychology, 68,* 159–169.

Cohen, S., Evans, G.W., Stokols, D., & Krantz, D.S. (1986). *Behavior, health and environmental stress.* New York: Plenum Press.

Cohen, S., Tyrrell, D.A.J., & Smith, A.P. (1991). Psychological stress and susceptibility to the common cold. *New England Journal of Medicine, 325,* 606–612.

Cohen, S., Tyrrell, D.A.J., & Smith, A.P. (1993). Life events, perceived stress, negative affect and susceptibility to the common cold. *Journal of Personality and Social Psychology, 64,* 131–140.

Cohen, S., & Williamson, G.M. (1991). Stress and infectious disease in humans. *Psychological Bulletin, 109,* 5–24.

Graham, N.M.H., Douglas, R.B., & Ryan, P. (1986). Stress and acute respiratory infection. *American Journal of Epidemiology, 124,* 389–401.

Herbert, T.B., & Cohen, S. (1993). Depression and immunity: A meta-analytic review. *Psychological Bulletin, 113,* 472–486.

Jabaaji, L., Grosheide, P.M., Heiftink, R.A., Duivenvoorden, H.J., Ballieux, R.E., & Vingergoets, A.J.J.M. (1993). Influence of perceived psychological stress and distress on antibody response to low dose rDNA hepatitis B vaccine. *Journal of Psychosomatic Research, 37,* 361–369.

Kiecolt-Glaser, J.K., Fisher, L.D., Ogrocki, P., Stout, J.C., Speicher, C.E., & Glaser, R. (1987). Marital quality, marital disruption, and immune function. *Psychosomatic Medicine, 49,* 13–34.

Kiecolt-Glaser, J.K., Garner, W., Speicher, C.E., Penn, G.M., Holliday, J., & Glaser, R. (1984). Psychosocial modifiers of immunocompetence in medical students. *Psychosomatic Medicine, 46,* 7–14.

Kiecolt-Glaser, J.K., Glaser, R., Shuttleworth, E.C., Dyer, C.S., Ogrocki, P., & Speicher, E. (1987). Chronic stress and immunity in family caregivers of Alzheimer's disease victims. *Psychosomatic Medicine, 49,* 523–535.

Lazarus, R.S., & Folkman, S. (1984). *Stress appraisal and coping.* New York: Springer.

Manuck, S.B., Cohen, S., Rabin, B.S., Muldoon, M., & Bachen, E. (1991). Individual differences in cellular immune response to stress. *Psychological Science, 2,* 111–115.

McKinnon, W., Weisse, C.S., Reynolds, C.P., Bowles, C.A., & Baum, A. (1989). Chronic stress, leukocyte subpopulations, and humoral response to latent viruses. *Health Psychology, 8,* 389–402.

Meyer, R.J., & Haggerty, R.J. (1962). Streptococcal infections in families. *Pediatrics, 29,* 539–549.

Rabin, B.S., Cohen, S., Ganguli, R., Lyle, D.T., & Cunnick, J.E. (1989). Bidirectional interaction between the central nervous system and immune system. *CRC Critical Reviews in Immunology, 9,* 279–312.

Stone, A.A., Bovbjerg, D.H., Neale, J.M., Napoli, A., Valdimarsdottir, H., Cox, D., Hayden, F.G., & Gwaltney, J.M. (1993). Development of common cold symptoms following experimental rhinovirus infection is related to prior stressful life events. *Behavioral Medicine, 8,* 115–120.

Stone, A.A., Cox, D.S., Valdimarsdottir, H., Jandorf, L., & Neale, J.M. (1987). Evidence that secretory IgA antibody is associated with daily mood. *Journal of Personality and Social Psychology, 52,* 988–993.

Stone, A.A., Neale, J.M., Cox, D.S., Napoli, A., Valdimarsdottir, H., & Kennedy-Moore, E. (1994). Daily events are associated with a secretory immune response to an oral antigen in men. *Health Psychology, 13,* 440–446.

Recommended Reading

Cohen, S., & Herbert, T.B. (1996). Psychological factors and physical disease from the perspective of human psychoneuroimmunology. *Annual Review of Psychology, 47,* 113–142.

Glaser, R., & Kiecolt-Glaser, J. (Eds.). (1994). *Handbook of human stress and immunity.* New York: Academic Press.

Possible Individuals in Language and Cognition

Paul Bloom[1]

Department of Psychology, University of Arizona, Tucson, Arizona

One approach to the psychology of proper names and count nouns explores the role these expressions play in our mental life. Proper names such as *Fido* correspond to entities we think of as individuals—entities that can be categorized, counted, and tracked over space and time. Count nouns such as *dog* correspond to kinds of individuals. It makes sense to talk of 2 dogs or 10 dogs, or to say that a certain dog is the same one that I saw yesterday, or to ask what happened to Fido. Not all parts of speech refer to individuals; adjectives like *big* and mass nouns like *water* do not correspond to entities that are countable or trackable in the same sense.

This observation raises the question of what sorts of entities are naturally thought of as individuals. We count, name, and track dogs—they are psychologically natural individuals. As a result, words that refer to this kind (*dog*) and words that refer to particular members of this kind (*Fido*) are easily learned by children. But not every logically possible individual is acceptable from the standpoint of human psychology. For instance, construing the spatially discontinuous entity composed of my dog and his favorite bone as a single individual is cognitively unnatural. We could not easily learn a proper name (*Fidobone,* say) for this entity, nor can we easily track it over space and time. Why is it that Fido is a psychologically possible individual, but Fidobone is not?

One answer is that Fido is a discrete physical object—and discrete physical objects are natural individuals. People count objects, track them, categorize them as belonging to different kinds, and learn names for these kinds. Psychologists typically concern themselves with objects when constructing theories of linguistic and nonlinguistic capacities, and many theories of how we learn and understand words are restricted to the learning and understanding of object names, implicitly adopting the view that, for humans, individuals just *are* discrete whole objects.

This view cannot be right, however. Children and adults do learn words such as *chapter, party,* and *joke;* we can count chapters, parties, and jokes; we can track them, categorize them, and so on. But to say that Jane wrote two chapters does not mean that she created two objects. If she goes to two parties on Saturday night, and tells two jokes at each party, what individuates the parties and jokes rests on subtle intentional factors, obvious enough intuitively, but difficult to specify precisely. What properties, if any, do these concepts share that make them all acceptable candidates for enumeration and naming? What makes these nonobject entities psychologically natural individuals?

This issue is not special to word learning. All theories of counting, categorization, and tracking must posit a domain over which these operations work, that is, a domain of individuals that get counted, categorized, and tracked. This domain cannot be limited to objects; many animals, including people, pigeons, and rats, are capable of quite complex computations over distinct sounds, events, and actions (see Wynn, 1992). A similar issue arises in social cognition. When we attribute mental states such as beliefs and goals, the targets of these attributions are not necessarily physical objects. We talk about a nation hesitating to take action, a hockey team seeking another chance for victory, and the Internal Revenue Service becoming concerned about one's home-office deduction. Such attributions