Psychological Stress, Immunity, and Upper Respiratory Infections
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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?

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., Jabaaiji 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, Kabin, Muldoon, & Bachen, 1991). Clinical depression has also been associated with decreased immune response (Herbert & Cohen, 1993).

**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). Verifcation 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). 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. 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-elicted 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. 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.

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-

![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.](image-url)
tious agent replicating (infection), or because stress increases the produc-
tion of histamines, bradyki-
nins, or other chemicals that trig-
ger symptoms after infection. In
this study, becoming biologically
infected was associated with high
levels of perceived stress and neg-
ative affect, but developing clinical
symptoms after infection was asso-
ciated with high numbers of
stressful life events. The fact that
these scales have independent re-
lations with clinical illness and that
these relations are mediated by
different biological processes chal-
enges the assumption that per-
ceptions of stress and negative af-
fact 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 in-
creased susceptibility had a rela-
tion independent of perceived
stress and negative affect (Stone et
al., 1993). As in our data, higher
numbers of stressful events were
associated with increased symp-
toms after infection.

A plausible explanation for the
direct association between stress-
ful 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 crit-
ical to influencing immune func-
tion and disease susceptibility.

In sum, there is substantial evi-
dence that both stressful life
events and psychological stress
(perceptions and negative affect)
influence susceptibility to upper
respiratory infections. These ef-
efforts are not a consequence of
unhealthy behaviors elicited by
stress. We also lack direct evidence
that increased susceptibility is at-
tributable to stress-induced immu-
nosuppression. The immune sys-
tem, however, is terribly complex,
and the measures used in human
studies may not adequately assess
the components most relevant to
resisting upper respiratory infec-
tions. Finally, contrary to accepted
stress and coping theory, the rela-
tion between stressful events and
susceptibility to infectious disease
does not depend on elevated per-
ceptions of stress and negative
emotional response.

CONCLUSIONS

The literature linking stress, im-
munity, and upper respiratory
infection is in many ways im-
pressive. First, it provides psy-
chologically 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 consist-
ent 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 respon-
sible for the link between stress
and disease susceptibility. Only by
identifying these pathways will re-
searchers be able to evaluate the
extent to which work with upper
respiratory viruses provides a ge-
neric model that will allow gen-
eralization to other infectious
agents.

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Notes

1. Address correspondence to Sheldon
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gie Mellon University, Pittsburgh, PA 15213.

2. Antibodies are protein molecules that
attach themselves to invading microorganisms and
mark them for destruction by our own immune sys-
tem. Each antibody recognizes only a single type of
microorganism.

3. The diseases caused by these viruses are
quite mild in the average old, null-stress partici-
pants, but they can cause serious illness in
immunocompromised individuals.

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 and therefore
will fight off a particular virus.

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Possible Individuals in Language and Cognition
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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 individuals 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
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