

It's Long-Term Stressors That Take a Toll: Comment on Cohen et al. (1998)

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In an extremely well-controlled study, Cohen et al. (1998) add to prior knowledge of stress–illness relationships by showing that self-reports of stress occurrence and duration of 1 month or more, rather than estimates of stressor severity, predict susceptibility to experimentally induced colds (i.e., viral replication and cold symptoms). Although ruling out obvious behavioral and personality factors as causes of the association of stressors to colds, they were unable to identify mediational immune factors, a deficit attributable to the difficulty of assessing the multi-layered, dynamic physiological processes within the bidirectional connections of the nervous (stress) and immune systems. The findings provide an interesting complement to data, showing that people use stressor duration in evaluating the illness implications of somatic symptoms (Cameron et al., 1995), and suggest caution with regard to overestimating the prevalence of stress-induced colds in natural settings.

Key words: acute stress, antibody, chronic stress, colds, epinephrine, life events, lymphocytes, natural killer cells, norepinephrine

The team of Cohen et al. (1998) provide an exceptionally detailed, empirical analysis of the relationship of life stress to illness. The study is exemplary for its care in defining both independent and dependent variables and for examining possible connecting pathways. The effort required to secure quality data from the large sample needed for these analyses deserves our applause. Where, however, do their findings leave us with regard to our understanding of the way in which life stress impacts health and with respect to their implications for the relationship of life stress to illness in more typical, nonlaboratory settings?

Pathways From Life Stress to Illness

To convince us that stressors have direct effects on illness requires that investigators define causal pathways at both the behavioral and physiological levels. Cohen et al. (1998) attempt this by carefully differentiating the significant class of stressors, chronic difficulties involving both interpersonal relationships and employment, and linking these specific stressors to the development of objectively defined colds, having both viral infection (viral culture or increased virus-specific antibody titer) and upper respiratory illness (increased mucus weight or mucociliary clearance). To

demonstrate that the stress effect is direct, they then rule out a number of alternative pathways commonly supposed to link stressful events to illness (for discussions see Cohen & Williamson, 1991; Contrada, Leventhal, & O'Leary, 1990; Maier, Watkins, & Fleshner, 1994; O'Leary, 1990). The list of health practices, such as smoking and exercise, and psychosocial factors, such as introversion and social network diversity, that contribute to the occurrence of illness is impressive; however, these factors do not account for the effect of life stress.

Having thus set the stage for identification of physiological paths that parallel the behavioral stress–illness link, Cohen et al. (1998) demonstrate relationships between colds and baseline measures of the neurotransmitters norepinephrine and epinephrine, whose stressor-specific alterations are well established (Covello, Pincomb, Brackett, & Wilson, 1990; Dimsdale & Moss, 1980; Lundberg & Frankenhauser, 1980) and often implicated in the mediation of stress-immune parameter alterations (Irwin, 1993; McEwen & Liebeskind, 1987) as well as the relationships of life stressors to two types of immunoreactive cells, helper T lymphocytes, and neutrophils. None of these physiological factors, however, could account for the relationship between life stressors and colds.

Given the broad range of neuroendocrine and immune parameters studied, the absence of a clear physiological pathway could be disappointing. However, the nature of neuroendocrine responses to stress and immunological responses to pathogens is multilayered and dynamic, and complexity of the homeostasis-maintaining bidirectional interactions within and between the two systems (Ader, Felton, & Cohen, 1990) renders the task of defining at the behavioral (stress–colds) and physiological levels anything but a simple matter.

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Viral replication and virus-specific antibody each reflect a different aspect of the infectious process (offensive and defensive) and together provide the medically accepted clinical definition of viral infection. However, given the interrelatedness of the host-response system, is it reasonable to expect immune parameters such as natural killer (NK) cell activity and helper T cell quantity to account for the relationship of life stress to colds when each may be affected (either directly or indirectly) by one of the dependent variables (i.e., virus-specific antibody, one of the markers of a cold)? If virus-specific antibody both defines the presence of a cold and minimizes the need for activation of helper T cells for some but not all participants, it reduces the likelihood that one will find helper T-cell number as the mediator of the link between stress and colds for the entire sample. Additionally, because 84% of Cohen et al.'s (1998) participants became virally infected and only 40% developed colds, stress and whatever may be presumed to mediate the stress-illness relationship were only predicting mucus weight and mucociliary clearance, the two determinants (in addition to viral infection) of having a cold, in the 40% of participants who actually developed colds. Are these two dependent variables the ones most likely to reflect the outcome of measures of cellular and humoral immune activity? Indeed, as Cohen et al. observe, it seems quite likely that there is more than one physiological process at work in the observed stress-illness relationship, a task that will necessarily involve the careful match of mediators to processes. These remarks are not offered as criticisms of Cohen et al.'s excellent work but as questions designed to bring out the difficulty of isolating causal pathways when one is dealing with a complex defense system and when investigators are virtually compelled to define their outcome (i.e., colds) with objective measures. Untangling these issues may require statistical analyses able to detect and summarize outcomes based on subject-specific patterns of response. Definition of the pathways may also be facilitated by examination of the reverse direction in the stress-illness pathway (i.e., that from illness and immune and endocrine activity to behavior; Leventhal, Patrick-Miller, Leventhal, & Burns, 1997; Maier, Watkins, & Fleshner, 1994). Understanding how disease-induced responses impact potential mediators of the stress-illness relationship would help with the selection of variables and the mode of analysis able to detect the mediational role of various components of the immune system.

External Validity of a Quasi-Experimental Clinical Trial

Although there is now little reason to doubt that severe chronic stressors can lower resistance to colds, Cohen et al.'s (1998) careful presentation makes clear that caution must be exercised in generalizing from their data to the broader question regarding the importance of stress as a determinant of illness in the natural environment. The first area for caution is the need to temper one's enthusiasm for generalizing the findings to chronic and/or life-threatening diseases. Cohen et al. clearly assert that chronic difficulties increase the likelihood of acquiring the common cold: This does not

imply that such stresses necessarily increase the likelihood of developing cancer or coronary disease. Each disease has its own complex physiological history and, unlike the common cold, may or may not be affected by the disturbances in the neuroendocrine and immune systems generated by chronic difficulties. Indeed, although the occurrence of acute stressors alone does not appear to increase susceptibility to the common cold, there is evidence that they may trigger episodes of coronary disease (Kamarck & Jennings, 1991). It is also important to note that, even though contact with the pathogenic virus was ensured in the study, only 40% of the participants developed a cold. If chronic disturbances were as likely to produce colds in the natural environment as in the trial, Cohen et al. might still be searching for participants who were chronically stressed and yet free of infection at baseline. Alternatively, the magnitude of the stress impact might vary considerably in persons older or less healthy than Cohen et al.'s volunteers.

It is also clear that the \$800 incentive for participation helped to recruit participants suffering from severe work stress, the difficulty producing the highest likelihood for developing a cold. Although job loss has been shown to create severe strains on the adaptive system (Kasl, 1978; Pearlin, Menaghan, Lieberman, & Mullan, 1981), including increased morbidity and mortality (Brenner, 1979), Cohen et al.'s (1998) findings provide a powerful example of one specific way that job loss may impact somatic well-being. Thus, Cohen et al. provide a classic example of how the very same factors can both maximize the internal validity of a study and increase the likelihood of showing that illness is a product of life difficulties and also raise questions and suggest limitations for external validity.

It is interesting to consider whether the relationship between chronic, but not acute, stressors and susceptibility to colds is congruent with commonsense beliefs about stress and illness. Our data on these beliefs provide an interesting connection to Cohen et al.'s (1998) findings. When faced with a recent life stress, our participants were likely to attribute vague (fatigue and other cold-like) symptoms to stress rather than to illness and were, consequently, unlikely to seek health care for these symptoms. When the life stressor lasted 1 month or longer, however, the rates of care seeking for vague symptoms increased to those found for signs and symptoms that were considerably more specific indicators of health problems (Cameron, Leventhal, & Leventhal, 1995). In this instance, it appears that commonsense corresponds, in part, to the realities documented by Cohen et al. We hope that Cohen et al. will further satisfy our interest in the relationship of self-observation and self-report to objective indicators (e.g., Diefenbach, Leventhal, Leventhal, & Patrick-Miller, 1996) by presenting the data on how closely participants' symptom reports and self-attributions of illness correspond to the "objective" signs of illness so carefully assessed in their study.

It is important to note that Cohen et al.'s (1998) approach to the assessment of life events, although relying on a detailed reporting of stressors and their context (Brown & Harris, 1989), ignores the participants' own appraisal of the severity of the event, information that is regarded as critical by ourselves and many others (Conrada, et al., 1990;

Dantzer, 1989; Henry, Stephens, & Ely, 1986; Lazarus & Folkman, 1984; Leventhal, Leventhal, & Contrada, 1998; Mason, Giller, Kosten, & Yehuda, 1990). Obtaining detailed reports and using judges to assess their impact on the "average person" seems to circumvent the various cognitive and affective processes that formulate the meaning of an event in individual lives. It appears, however, to provide a valid representation of stressor impact and raises an interesting finding (i.e., that a concurrent acute event reduces the likelihood of colds in persons experiencing chronic difficulties). As Cohen et al. indicate, although the finding is "borderline" in the statistical sense, it merits comment both because it parallels findings in the mental health literature (McGonagle & Kessler, 1990) and because the Cohen et al. study adopted so detailed an approach to the assessment of difficulties and events. Why might acute stressors decrease the impact of a chronic difficulty when most theoretical analyses would likely regard the former as a source of increased stress (Lazarus & Folkman, 1984)? One possibility is that acute stressors are physiologically activating and indeed have often been associated with increases in some immune parameters, particularly those associated with the most primitive forms of host resistance (e.g., NK cells; Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992). Another possibility, suggested by Cohen et al., is that acute events may be a distraction from chronic life difficulties. It is also possible that acute events provide an opportunity for effective problem solving, which enhances self-efficacy and self-esteem. It would be interesting to determine whether the protective value of an acute, controllable event is enhanced if it is perceived as being linked to a chronic life difficulty, because its solution may suggest that the difficulty itself will eventually be controllable. This is clearly an area for further investigation.

In summary, Cohen et al. (1998) provide powerful validation of one of our most cherished hypotheses: that life stress can damage one's health. Although the extent of damage may be limited, as in the case of increased susceptibility to the common cold, it will encourage further imaginative use of our most powerful tools to assess the possibility of similar effects for chronic and life-threatening illnesses.

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