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Stress, Reactivity, and Disease

[Editorial Comment]

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Outline

The proposition that stress plays a role in the etiology and progression of a broad range of physical diseases is a basic assumption in psychosomatic medicine. However, convincing evidence that stress contributes to the pathophysiology of human disease is sparse, and, even where evidence exists, relatively small proportions of variance are explained. One response to this dilemma has been to hypothesize stress accentuators or buffers, also referred to as vulnerability factors. These are characteristics that are perceived to render individuals (or groups of individuals) more or less vulnerable in the face of stressful events. They include personal ([1]), social ([2]), and biological characteristics ([3]). In theory, when we are able to characterize individual vulnerability successfully, we will be able to establish a stress-disease relationship more definitively. Because the cardiovascular and immune systems are implicated in a number of disease processes, individual differences in the magnitude of these systems' responses to stressful events ("reactivity") are prime candidates for vulnerability factors. This assumption is at the core of the article by Boyce and his colleagues ([4]) reported in this issue.

Unlike earlier investigators, Boyce et al. do not conceptually distinguish between cardiovascular and immune reactivity but rather propose a unified "psychobiologic reactivity" as a potential vulnerability factor. Their argument for a unified response is based on evidence for associations (although not substantial) between cardiovascular and certain immune responses to stress, including phytohemagglutinin (PHA)- and concanavalin A (ConA)-stimulated lymphocyte proliferation and the number of CD8 (T-suppressor/cytotoxic) and CD15/56 (natural killer) cells in circulation ([5-7]). This assumption allows the hypothesis that cardiovascular (and immune) reactivity might moderate the impact of stressful events on susceptibility to upper respiratory infections.

Boyce and his colleagues report an ambitious set of studies that took on many practical and conceptually difficult problems. To start with, the subjects were 3- to 5-year-old children. Measurement of reactivity in such samples is challenging. The collection of cardiovascular responses to multiple stressors in the first study provides a model of how assessment of reactivity in children can be done. Probably because it requires drawing blood at least twice, measurement of immune reactivity in children has not previously been reported. Boyce and his colleagues not only collected blood to assess response to a stressor but also assayed the blood samples for a range of immune responses. Respiratory tract examinations by nurses in the first study also provided a "verified" disease measure. This avoids confusing changes in pathophysiology with changes in attentional and perceptual processes that influence symptom recognition and reporting ([8]).

The principal hypothesis of the Boyce et al. study was that "individual differences in psychobiologic stress reactivity would moderate previously observed associations between psychological stress and respiratory illness" (418). Boyce and his colleagues found that children showing the largest stress-induced increases in cardiovascular response (Study I) and children showing the greatest stress-induced increases in circulating B cells and (marginally) pokeweed mitogen-stimulated lymphocyte proliferation (Study II) were at greater risk for developing upper respiratory infections in response to an environmental stressor. Although not entirely consistent with the logic of their arguments (e.g., one would expect those with the greatest decrease in proliferation to be at greatest risk), they suggest that these data are consistent with the hypothesis that both cardiovascular and immune reactivity moderate stress-induced effects on host resistance. Totally unexpectedly, they also found that reactive children demonstrated fewer upper respiratory infections then all other children when they experienced relatively lower levels of stress. The stress-by-reactivity interaction that was the basis for their conclusions was found for only one of two stressor measures in each study, and the stress-by-immune reactivity interaction was found for only two (one marginally) of the four immune measures. The authors conclude that "subgroups of children exist that sustain hyperdynamic biological responses to psychologically stressful events and experiences... such children might be expected to encounter poorer health in high stress contexts and unusually positive health outcomes in low stress contexts" (419).

These results help to highlight some common assumptions in the reactivity literature that are rarely addressed directly. However, the studies themselves are not without limitations. Many of these problems are addressed by the authors in the discussion section of the article. Rather than provide a methodological critique of this work, we thought it more productive to address four conclusions that readers might from the article and discuss whether or not they are valid ones.

IMMUNE AND CARDIOVASCULAR RESPONSES TO STRESSORS ARE RELATIVELY STABLE DISPOSITIONS THAT ARE REPLICABLE OVER TIME AND ACROSS DIFFERENT STRESSFUL EVENTS^

Conceptualization of "reactivity" as an enduring trait implies that response differences among people are reproducible on successive occasions of measurement and under varying stimulus conditions. Such consistency long eluded demonstration in the cardiovascular area because of a predominance in this literature of "single task-single session" protocols and their inherent limitations as instruments for trait assessment (i.e., analogous to one-item tests of personality). However, recent studies indicate that high test reliability can be achieved by aggregating responses across multiple stimuli and, even more so, by aggregating over multiple tasks administered on multiple occasions (e.g., yielding generalizability coefficients typically above.80) ([9,10]). In consequence, there is now convincing evidence that cardiovascular reactivity constitutes a stable dimension of individual difference.

The status of the concept of dispositional immune reactivity is more tenuous. First, the immune system is highly differentiated, and consequently immune measures are not often intercorrelated. Hence, it makes more sense to focus on the reactivity of single immune measures (or clusters of measures) that represent specific processes than to hypothesize a unidimensional immune responsiveness. Interest in the reactivity of specific measures is further enhanced to the extent that it is biologically plausible that the process being assessed plays a role in the

development or progression of infectious disease. Second, little is known about the test-retest reliabilities of immune responses to stress. Although recent evidence suggest reasonable test-retest reliabilities in stress-induced changes in PHA-stimulated blastogenesis and numbers of CD8 and CD56 cells in circulation, other stress-induced immune changes (e.g., ConA-stimulated blastogenesis) were not reliable ([11]). Until the reliabilities of range of immune measures are established, it is premature to conclude that immune reactions to stress, like those of heart rate and blood pressure, reflect dispositional attributes of individuals.

THERE IS A COMMON COORDINATED BIOLOGICAL RESPONSE THAT CAN BE MEASURED EQUIVALENTLY THROUGH CARDIOVASCULAR OR IMMUNE REACTIVITY^

It is widely believed that individual differences in cardiovascular response and immune reactivity stem from a common source from which it follows that response distributions generated by the two systems should correlate highly. Unfortunately, the investigators present no evidence of such a relationship. There are, however, several studies in which some (but not other) immune responses to stress are moderately correlated with concomitant cardiovascular reactions and changes in plasma catecholamine concentrations ([5-7]). The latter findings, together with results of agonist infusion and receptor blocking studies, suggest that cardiovascular and immune reactivity may, in part, reflect an underlying distribution of individual differences in stress-induced sympathoadrenal activation ([11,12]). Beyond this limited sphere of shared variance, however, each system is surely responsive to a variety of specific and unrelated mechanistic influences, which may also differ among individuals and contribute to reactivity-disease associations.

In sum, there may be a common "psychobiologic reactivity" to stress, which is manifested in concomitantly influenced but only partially correlated cardiovascular and immune responses. However, there is need to determine exactly which immune processes share this common pathway before such a hypothesis could be adequately addressed.

DISPOSITIONAL CARDIOVASCULAR REACTIVITY AND DISPOSITIONAL IMMUNE REACTIVITY HAVE IMPLICATIONS FOR STRESS-INDUCED PATHOPHYSIOLOGY OF UPPER RESPIRATORY INFECTIONS^

Although Boyce et al. do not articulate an explicit model of reactivity-disease associations, the most logical "mechanistic" hypotheses are that these peripheral manifestations of physiologic reactivity alter physiological responses to stress that confer an increased succeptibility to infection; or alter behavioral responses to stress that increase the probability of exposure to infectious agents. Because reactivity has traditionally been linked to disease through direct physiological effects, our discussion focuses on physiological processes that would result in increased susceptibility to infection. However, an argument that physiologically reactive children differ in their interpersonal behaviors under low and high stress and that these differences influence their risk for exposure is every bit as plausible as the argument for direct physiological effects.

If we adopt the hypothesis of a directly conferred decrease in host resistance, then the immune reactivity measured in Study II must be considered most proximate to the outcome of interest and, therefore, the putative mechanism for stress-upper respiratory infection associations. In this context, measures of cardiovascular reactivity, as in Study I, are used essentially as proxies for immune reactivity, and immune reactivity is used as a marker of host resistance to viral infections. The legitimacy of the assumptions outlined above rests on a) the degree to which cardiovascular and immune responses correlated by virtue of a common origin and b) the degree to which the specific forms of immune reactivity assessed in this study are important for host resistance. Unfortunately, previously published studies generally do not find correlations between cardiovascular response and changes in B cells or pokeweed mitogen-stimulated blastogenesis ([5,6]), suggesting the need for cautious interpretation of the current results. Moreover, although plausible arguments could be made linking these immune responses to host resistance, there are no data addressing this issue, and it may be oversimplistic to

assume that reactivity of any single immune measure assessed at an arbitrary point in time (in relation to exposure to a pathogen) would predict host resistance ([14]).

DISPOSITIONAL REACTIVITY RESULTS IN UNUSUALLY POSITIVE HEALTH OUTCOMES UNDER RELATIVELY LOW LEVELS OF STRESS^

As mentioned earlier, a lower incidence of disease for reactive children under low stress was an unexpected result. It does not conform to either psychological or biological theories of the nature of the stress-disease relation. Although in the discussion section the authors describe several studies reporting similar interactions in the prediction of psychological outcomes, we do not know of any similar data from studies of physiological outcomes. Most importantly, in the absence of any known physiological mechanism that could account for the effect, these results must be viewed as preliminary and the authors' conclusions as speculative.

SUMMARY^

In summary, this work is an ambitious attempt to address some key issues in regard to the clinical importance of reactivity. The authors should be complimented for their efforts in addressing these issues, especially in small children. However, it is necessary to view their data in light of both the studies' strengths and weaknesses and to evaluated the implications of the work in light of existing theory and evidence. From this perspective, we think the work provokes interesting ways to think about reactivity. However, it leaves to subsequent research the task of systematically addressing the many issues that it raises.

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