

Psychoneuroimmunology

Psychology's Gateway to the Biomedical Future

Janice K. Kiecolt-Glaser

Department of Psychiatry and the Institute for Behavioral Medicine Research, Ohio State University College of Medicine

ABSTRACT—*How do stressful events and negative emotions influence the immune system, and how big are the effects? This broad question has been intensely interesting to psychoneuroimmunology researchers over the last 3 decades. Many promising lines of work underscore the reasons why this question is still so important and pivotal to understanding and other advances. New multidisciplinary permutations provide fresh vistas and emphasize the importance of training psychologists more broadly so that they will be central and essential players in the advancement of biomedical science.*

How do stressful events and negative emotions influence the immune system, and how big are the effects? This broad question has been intensely interesting to psychoneuroimmunology (PNI) researchers over the last 3 decades, and the consequent discoveries have substantially changed the face of health psychology. We have learned that distress can slow wound healing, diminish the strength of immune responses to vaccines, enhance susceptibility to infectious agents, and reactivate latent viruses (Glaser & Kiecolt-Glaser, 2005). Moreover, stress and depression can also substantially augment the production of proinflammatory cytokines that are associated with a spectrum of age-related diseases (Kiecolt-Glaser et al., 2003). Indeed, it is precisely because PNI researchers' efforts have been so fruitful that we can now glimpse just how exciting and far reaching the answers can be. In this article, I briefly describe several promising lines of work that underscore the reasons why this question is still so important and pivotal to understanding and other advances. I also suggest that new multidisciplinary permutations will provide fresh vistas in the field. Finally, I argue that we need to train our students more broadly to assure that they—and our discipline—will be not only competitive, but essential players in the advancement of biomedical science.

Address correspondence to Janice K. Kiecolt-Glaser, Department of Psychiatry, Ohio State University College of Medicine, 1670 Upham Drive, Columbus, OH 43210; e-mail: Kiecolt-Glaser.1@osu.edu.

STRESS DYSREGULATES THE IMMUNE SYSTEM AND COMPROMISES HEALTH

Vaccines

A series of studies have demonstrated that immune responses to viral and bacterial vaccines are delayed, substantially weakened, and/or shorter lived in stressed or distressed individuals (Glaser & Kiecolt-Glaser, 2005). Vaccine responses are important because they reflect protection or the lack thereof; in addition, they also demonstrate clinically relevant alterations in immune responses to challenge under well-controlled conditions, providing a proxy for responses to infectious agents. The evidence that stress and distress impair vaccine responses has obvious public health relevance because infectious diseases can be so deadly; indeed, infectious disease epidemics are always a threat, as has been well illustrated in recent years by the severe acute respiratory syndrome (SARS) and the Asian bird flu.

Furthermore, the human papillomavirus (HPV) vaccine was the first of a series of new vaccines developed to target etiologic agents for certain cancers. Researchers were particularly interested by the evidence that greater perceived stress was associated with a poorer HPV-specific immune response in women with cervical dysplasia (Fang et al., 2008); these data strongly support the hypothesis that both antibody and T-cell immunity to the HPV vaccine could be adversely affected by stress, significantly impairing the vaccine's efficacy.

Despite the public health relevance, the fact that vaccine efficacy can be compromised by stress does not seem to have received much attention in the biomedical community to date. The infectious disease and cancer vaccines offer new arenas for demonstrating the importance of behavioral influences on immune function.

Inflammation

Research from the last decade has established the immune system's central role in age-related diseases. Proinflammatory cytokines such as interleukin-6 (IL-6) play a key role in cardiovascular disease, the leading cause of death, as well as Type II diabetes, arthritis, osteoporosis, Alzheimer's disease,

periodontal disease, some cancers, and frailty and functional decline (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002).

Negative emotions like depression and anxiety enhance the production of proinflammatory cytokines, as do psychological stressors (Lutgendorf et al., 1999; Segerstrom & Miller, 2004). In addition, stress and depression also contribute to a greater risk for infection, prolonged infectious episodes, and delayed wound healing—all of which are processes that can fuel sustained proinflammatory cytokine production (Glaser & Kiecolt-Glaser, 2005).

Not surprisingly, chronic stressors take a toll: A longitudinal study showed that the average annual rate of increase in serum IL-6 was about four times larger in men and women who were chronically stressed by caregiving for a spouse with dementia than it was in similar individuals who did not have caregiving responsibilities (Kiecolt-Glaser et al., 2003). Moreover, the mean annual changes in IL-6 among former caregivers did not differ from that of current caregivers, even several years after the death of the impaired spouse, suggesting that chronic stress might prematurely age the immune response. Recent data suggest that stress and depression can influence cytokine secretion by tumor cells that influence the tumor microenvironment via neuroendocrine pathways (Antoni et al., 2006). These stress-related changes in inflammation provide evidence of one mechanism through which stressors may accelerate risk of a host of age-related diseases.

MULTIDISCIPLINARY OPPORTUNITIES

The stress-related changes in inflammation are part of the growing evidence that both stress and depression augment the adverse effects of aging on immune function (Coe & Lubach, 2003; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996). However, viewed from another perspective, the evidence that vulnerabilities are not merely additive provides a window for considering new multidisciplinary prospects.

For example, consider the possible intersections of stress/depression, diet, and immune function. Arachidonic-acid-derived (ω -6 or n -6) eicosanoids (primarily from refined vegetable oils such as corn, sunflower, and safflower) increase the production of proinflammatory cytokines (van West & Maes, 2003). In contrast, the ω -3 (n -3) polyunsaturated fatty acids found in fish, fish oil, walnuts, wheat germ, and some dietary supplements such as flax seed products can curb the production of arachidonic-acid-derived eicosanoids (Pischoon et al., 2003). Thus, higher n -6: n -3 ratios promote proinflammatory cytokine production (Pischoon et al., 2003). It is important to note that individuals with high n -6: n -3 ratios may also produce greater increases in proinflammatory cytokine production during stressful times (Kiecolt-Glaser et al., 2007; Maes, Christophe, Bosmans, Lin, & Neels, 2000). Furthermore, higher levels of syndromal depression and depressive symptoms are associated with higher n -6: n -3 ratios, and n -3 supplementation may have

positive effects on mood and inflammation (Hibbeln, Nieminen, Blasbalg, Riggs, & Lands, 2006; Maes et al., 2000). Clearly, these key dietary pathways have implications for both psychological and immunological responses, as well as their interaction.

As another example, immunotoxicology addresses the potential deleterious effects of environmental toxicants such as pesticides or air and water pollution on the immune system (Friedman & Lawrence, 2002). Immune dysregulation associated with immunotoxicant exposure may be exacerbated in depressed or stressed individuals, thereby increasing the risk for adverse health outcomes. These effects are likely to be most evident in more vulnerable groups such as children and older adults (Coe & Lubach, 2003), and they may enhance risk for illnesses including allergy and asthma, viral infections, and cancer. Indeed, there is evidence that the effects of traffic-related air pollution and exposure to violence may synergistically promote the development of asthma in children (Clougherty et al., 2007).

In fact, researchers have speculated that the poorer health associated with lower socioeconomic status and/or marginalized populations may result from greater exposure to indoor allergens (cockroach and mouse allergens) as well as toxicants (lead-based paint) and irritants and pollutants such as tobacco smoke and diesel-related particles (Friedman & Lawrence, 2002; Wright & Subramanian, 2007). Further research addressing how psychological, biological, and environmental risks intersect and interact is clearly needed.

WHAT MORE SHOULD THE FIELD BE DOING TO ANSWER THE QUESTION?

We need to put greater emphasis on cross-discipline training for our students, underscoring the importance of getting a strong foundation in basic biological science. To communicate effectively with the biomedical and basic science communities, we need to understand and speak basic biology and physiology, and we need to understand key fundamental immunological concepts. Realistically, psychologists are more likely to see the value and importance of cross-discipline work more clearly than would most of our biomedical and basic science collaborators at this point in time, and thus the onus is on us to initiate the conversations. Failure to forge strong cross-discipline collaborations will mean that our small share of NIH funding will diminish even further; NIH's transdisciplinary and translational science roadmap prominently highlights this issue.

In fact, it is much easier for a psychologist to learn sufficient basic immunology to competently design reasonable collaborative PNI studies than it is for an immunologist to get a basic background in behavioral science. If you doubt this premise, consider the breadth of the key foundational knowledge needed to design a simple behavioral study with any hope of publication; a researcher needs to have more than a nodding acquaintance with experimental design, basic statistics, some knowledge of

measurement theory/practice, and much more. Furthermore, cross-discipline training will help us see the broader interdisciplinary collaborative possibilities.

How do stressful events and negative emotions influence the immune system, and how big are the effects? The answers to this key question will certainly advance psychology in general as well as PNI and health psychology; by providing key data on how stressful events and the emotions they evoke get translated into health, psychology will assume a more dominant role in the health sciences, in health promotion, and in public health policy. Our voice and our contributions will be louder, stronger, and more forceful.

Acknowledgments—Work on this article was supported in part by National Institute of Health Grants AG029562, CA126857, AT003912, and CA131029.

REFERENCES

- Antoni, M.H., Lutgendorf, S.K., Cole, S.W., Dhabhar, F.S., Sephton, S.E., McDonald, P.G., et al. (2006). The influence of bio-behavioural factors on tumour biology: Pathways and mechanisms. *Nature Reviews Cancer*, *6*, 240–248.
- Clougherty, J.E., Levy, J.I., Kubzansky, L.D., Ryan, P.B., Suglia, S.F., Canner, M.J., et al. (2007). Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environmental Health Perspectives*, *115*, 1140–1146.
- Coe, C.L., & Lubach, G.R. (2003). Critical periods of special health relevance for psychoneuroimmunology. *Brain, Behavior, and Immunity*, *17*, 3–12.
- Fang, C.Y., Miller, S.M., Bovbjerg, D.H., Bergman, C., Edelson, M.I., Rosenblum, N.G., et al. (2008). Perceived stress is associated with impaired T-cell response to HPV16 in women with cervical dysplasia. *Annals of Behavioral Medicine*, *35*, 87–96.
- Friedman, E.M., & Lawrence, D.A. (2002). Environmental stress mediates changes in neuroimmunological interactions. *Toxicological Sciences*, *67*, 4–10.
- Glaser, R., & Kiecolt-Glaser, J.K. (2005). Stress-induced immune dysfunction: Implications for health. *Nature Reviews Immunology*, *5*, 243–251.
- Hibbeln, J.R., Nieminen, L., Blasbalg, T.L., Riggs, J., & Lands, W.E. (2006). Healthy intakes of n-3 and n-6 fatty acids: Estimations considering worldwide diversity. *American Journal of Clinical Nutrition*, *83*, 1483S–1493S.
- Kiecolt-Glaser, J.K., Belury, M.A., Porter, K., Beversdorf, D., Lemeshow, S., & Glaser, R. (2007). Depressive symptoms, omega-6: omega-3 fatty acids, and inflammation in older adults. *Psychosomatic Medicine*, *69*, 217–224.
- Kiecolt-Glaser, J.K., Glaser, R., Gravenstein, S., Malarkey, W.B., & Sheridan, J. (1996). Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proceedings of the National Academy of Sciences, USA*, *93*, 3043–3047.
- Kiecolt-Glaser, J.K., McGuire, L., Robles, T.R., & Glaser, R. (2002). Emotions, morbidity, and mortality: New perspectives from psychoneuroimmunology. *Annual Review of Psychology*, *53*, 83–107.
- Kiecolt-Glaser, J.K., Preacher, K.J., MacCallum, R.C., Atkinson, C., Malarkey, W.B., & Glaser, R. (2003). Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National Academy of Sciences, USA*, *100*, 9090–9095.
- Lutgendorf, S.K., Garand, L., Buckwalter, K.C., Reimer, T.T., Hong, S., & Lubaroff, D.M. (1999). Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. *Journals of Gerontology: Series A. Biological Sciences and Medical Sciences*, *54*, M434–M439.
- Maes, M., Christophe, A., Bosmans, E., Lin, A.H., & Neels, H. (2000). In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychologic stress. *Biological Psychiatry*, *47*, 910–920.
- Pischon, T., Hankinson, S.E., Hotamisligil, G.S., Rifai, N., Willett, W.C., & Rimm, E.B. (2003). Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among U.S. men and women. *Circulation*, *108*, 155–160.
- Segerstrom, S.C., & Miller, G.E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*, *130*, 1–37.
- van West, D., & Maes, M. (2003). Polyunsaturated fatty acids in depression. *Acta Neuropsychiatrica*, *15*, 15–21.
- Wright, R.J., & Subramanian, S.V. (2007). Advancing a multilevel framework for epidemiologic research on asthma disparities. *Chest*, *132*(Suppl.), 757S–769S.