Turning Up the Heat

Inflammation as a Mechanism Linking Chronic Stress, Depression, and Heart Disease

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ABSTRACT—*Mounting evidence indicates that chronic stressors and depressive symptoms contribute to morbidity and mortality from cardiac disease. However, little is known about the underlying mechanisms responsible for these effects or about why depressive symptoms and cardiac disease co-occur so frequently. In this article we outline a novel model that seeks to address these issues. It asserts that chronic stressors activate the immune system in a way that leads to persistent inflammation. With long-term exposure to the products of inflammation, people develop symptoms of depression and experience progression of atherosclerosis, the pathologic condition that underlies cardiac disease.*

KEYWORDS—*stress; depression; inflammation; atherosclerosis*

Though people have long believed that certain thoughts and feelings are toxic for their health, only in the past 30 years has convincing evidence accumulated to support this view. This research indicates that while not all negative thoughts and feelings are bad for health, specific cognitive and emotional processes do contribute to the development and progression of medical illness. In this article we focus on two of the best-studied culprits, chronic stressors and depressive symptoms, and how they "get under the skin" to influence disease. We focus on coronary heart disease (CHD), the leading cause of mortality in developed countries and the context in which mind–body connections are best documented.

STRESSORS, DEPRESSION, AND CHD RISK

Chronic stressors come in different packages, ranging from troubled marriages to difficult workplaces. What they have in common is the tendency to be appraised as threatening and unmanageable. They can involve situations in which the troubling stimulus persists over a long time (an abusive boss), as well as situations in which the event is brief but the threat persists longer (a sexual assault). Research indicates that exposure to chronic stress generally increases vulnerability to CHD. In a study of 12,000 healthy males followed over 9 years, those facing chronic difficulties at work or home were 30% more likely to die of CHD (Matthews & Gump, 2002). Another project measured adverse childhood experiences in 17,000 adults and found a dose–response relationship with CHD incidence. Those who reported a variety of adverse experiences such as neglect, domestic violence, and parental criminal behavior were 3.1 times more likely to develop CHD (Dong et al., 2004).

Depression can take the form of a low mood or a clinical syndrome. In both cases it typically involves sadness and anhedonia, which may be accompanied by disturbances in eating, sleeping, and cognition. Depression is common in CHD. About 20% of patients meet criteria for a clinical diagnosis, and even more have symptoms below the diagnostic threshold. These symptoms diminish quality of life and contribute to poorer medical outcomes. For example, in a study of 900 patients interviewed in the hospital following a heart attack, high levels of depressive symptoms were associated with a threefold increase in cardiac mortality over 5 years (Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002). There is also evidence that in healthy young adults, depressive symptoms can accelerate the development of CHD. For example, in a 27-year study of middle-aged adults, those with high levels of depressive symptoms at baseline were 1.7 times more likely to have a fatal heart attack (Barefoot & Schroll, 1996).

Although these findings provide compelling evidence of mind–body connections in CHD, they also raise challenging questions that researchers are just starting to address. One has to do with the underlying mechanisms linking mind and body. How can nebulous patterns of thinking and feeling "get inside the body" in a way that alters disease trajectories? A second question has to do with the high rate of comorbidity between depression and CHD. There are other serious medical condi-

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tions, such as cancer, for which the rates of depression are much lower (Dew, 1998). Why is it especially common in cardiac patients? Another question researchers struggle with concerns theoretical integration. Though most studies have focused on chronic stress or depressive symptoms, these states are likely to be closely related and to influence disease through similar pathways. So an important challenge involves conceptually integrating literatures that have evolved separately and determining where the "action" really is.

AN INTEGRATIVE CONCEPTUAL FRAMEWORK

We have developed a conceptual framework to begin answering these questions (Fig. 1). It begins with the notion that chronic stressors activate the immune system in a way that leads to persistent inflammation. This refers to a molecular and cellular cascade the body uses to eliminate infections and resolve injuries. The model suggests that with long-term exposure to the products of inflammation, people develop symptoms of depression and experience accelerated CHD progression. This occurs because the signaling molecules deployed to orchestrate inflammation—pro-inflammatory cytokines—elicit adaptations in the brain that are manifested as symptoms of depression. These molecules also promote growth of plaques in blood vessels and stimulate processes that lead those plaques to rupture. In doing so, they bring about heart attacks. The model goes on to assert that the excessive inflammation is responsible for bidirectional connections between depression and atherosclerosis. That is, cytokines are viewed as a mechanism through which depression fosters CHD progression, and at the same time as the reason cardiac patients experience high rates of affective difficulties. It should be noted that although chronic stress is depicted as the model's starting point, a person could enter the cascade as a result of depressive symptoms or coronary disease; chronic stress is sufficient, but not necessary, to initiate the model's processes.

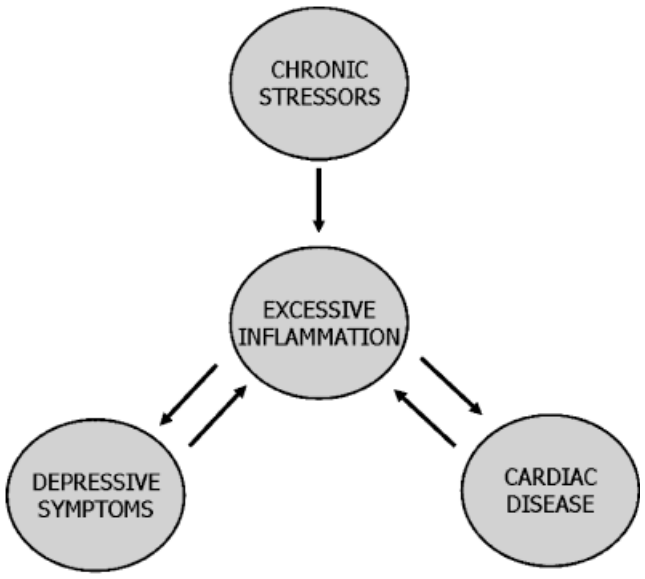

Fig. 1. Model of how inflammatory processes mediate the relations among chronic stressors, depressive symptoms, and cardiac disease. Stressors activate the immune system in a way that leads to persistent inflammation. With long-term exposure to the molecular products of inflammation, people are expected develop symptoms of depression and experience progression of cardiac disease. Excessive inflammation is also viewed as responsible for the bidirectional relationship between depression and atherosclerosis. (Some pathways in the model are excluded for the sake of brevity and simplicity—for example, the likely bidirectional relationship between chronic stressors and depressive symptoms.

WHAT IS INFLAMMATION?

When the immune system detects invading microbes like viruses or bacteria, it launches an inflammatory response, which causes white blood cells to accumulate at the site of infection. These cells attempt to eliminate the pathogen, rid the body of cells that have been infected with it, and repair any tissue damage that it has caused. This entire process is orchestrated by inflammatory cytokines, which are signaling molecules secreted by white blood cells. The most critical cytokines are interleukin-1β, interleukin-6 (IL-6), and tumor necrosis factor-α, and they have wide-ranging functions that include directing cells toward infections, signaling them to divide, and activating their killing mechanisms. Because these molecules are released when the immune system is active, researchers use their presence as a rough index of the magnitude of inflammation in the body. This is also done by measuring C-reactive protein (CRP), a molecule produced by the liver in response to IL-6.

DOES CHRONIC STRESS TRIGGER INFLAMMATION?

What evidence is there to support the idea that chronic stressors activate the immune system in a way that promotes inflammation? Over the past few years a number of studies have found that among persons facing serious chronic stressors, concentrations of inflammatory molecules such as IL-6 and CRP are significantly elevated (Segerstrom & Miller, 2004). One project followed older adults caring for a relative with dementia. Caregiving is a potent chronic stressor that presents challenges in nearly every domain of life, and it does so at a time of life when coping resources are often waning. Over a 6-year follow-up, caregivers displayed marked increases in IL-6 and did so at a rate that was four times more rapid than controls (Kiecolt-Glaser et al., 2003). This pattern of findings was initially puzzling to researchers, because chronic stressors were believed to suppress immune functions. But it is now clear that the immune system responds to any given stressor in a complex fashion; some of its functions are activated at the same time as others are disabled (Segerstrom & Miller, 2004).

Researchers are now seeking to understand the mechanisms through which chronic stressors bring about inflammation. Some evidence indicates that chronic stressors "prime" the immune system to respond to challenges in an especially aggressive

fashion. Another hypothesis is that chronic stressors interfere with the immune system's capacity to shut down after a challenge has been minimized. One signal the body uses to do this is cortisol; at high levels, this hormone dampens the release of cytokines. However, chronic stressors interfere with this process. In parents whose children were being treated for cancer, for example, cortisol's ability to suppress IL-6 production was markedly diminished (Miller, Cohen, & Ritchey, 2002). This suggests that chronic stressors "take the brakes off" inflammation. Another intriguing possibility derives from animal research showing that stressors like social isolation can bring about inflammation in the brain (Maier, Watkins, & Nance, 2001). This process has been shown, in turn, to activate inflammation in the periphery. So, in humans, chronic stressors may trigger a cytokine cascade that starts in the brain and then makes its way to other areas of the body.

DEPRESSION AND INFLAMMATION

Can inflammation bring about depression? To answer this question, researchers have exposed rodents to bacterial products that trigger inflammation and shown that the animals develop symptoms resembling depression—symptoms known as "sickness behaviors." These include declines in food intake, motor activity, grooming behavior, and social exploration, as well as a lack of interest in hedonic activities such as sex (Yirmiya, 1996). It has been difficult to examine this process directly in humans, because they cannot safely be exposed to inflammatory substances. However, researchers have been able to address this question indirectly in cancer patients, who are administered cytokines with the hope that they will boost immune functions. About 50% of patients treated with cytokines develop symptoms, such as dysphoria, anhedonia, fatigue, anorexia, and cognitive impairment, that are consistent with a diagnosis of major depression (Musselman et al., 2001). The extent of these symptoms is directly related to the dose of cytokine therapy, and prophylactic treatment with antidepressant medications can often prevent them from arising. Although these findings suggest that inflammation brings about adaptations that resemble depression, further research is necessary to determine whether these conditions are one and the same or merely "look-alikes." It may also be the case that sickness behavior underlies some cases of depression—like those that arise in CHD and other inflammatory conditions—but is not responsible for affective difficulties more generally.

Researchers are still attempting to understand how and why sickness behaviors emerge. They may be an evolved strategy to maximize the chances of survival after infection (Maier & Watkins, 1998). When infected, an organism's survival depends on its capacity to mount a vigorous defense and to avoid contact with pathogens and predators that might capitalize on its vulnerability. Organisms must initiate a febrile response, which interferes with pathogens' capacity to reproduce, and mobilize their immune systems to fight. These responses, however, pose significant metabolic demands. By spending more time sleeping and withdrawing from activities, the organism conserves energy and avoids contact with pathogens and predators. When viewed from this perspective, the "depressive" symptoms that arise following inflammation are behavioral adaptations that evolved to maximize the chances of survival during infection.

And can depression provoke inflammation? Cross-sectional studies indicate that among patients suffering from clinical depression, concentrations of CRP and IL-6 are increased by 40% to 50% (Miller, Stetler, Carney, Freedland, & Banks, 2002). These effects do not seem to be limited to clinical depression; similar patterns are found in patients with depressive symptoms, even when they are not severe enough to warrant a diagnosis. But it is difficult to rigorously evaluate whether depression provokes inflammation, because humans cannot be randomly assigned to experience affective difficulties. To overcome this difficulty, researchers have studied patients before and after treatment and have shown that cytokine volumes decrease after depressive symptoms have been ameliorated. These findings suggest that depression operates causally. How it does so remains unclear. Depressive symptoms could prime the immune system to respond aggressively to challenges; alternatively, they could initiate a cytokine cascade in the brain that spreads elsewhere. They also could foster maladaptive behaviors that themselves activate inflammatory processes. The best data to date are consistent with the latter hypothesis; much of the inflammation in depression is attributable to excess weight and sleeping disturbances (Miller, Stetler, et al., 2002; Motivala & Irwin, in press).

INFLAMMATION CONTRIBUTES TO CHD

CHD begins when infections and injuries damage the arteries supplying the heart, causing an influx of white blood cells that are seeking to repair the lesion. These cells accumulate in the vessel wall, where they become engorged with cholesterol, and eventually contribute to formation of plaque. Much later in the disease process, these cells help to destabilize the plaque. When this occurs, the plaque can rupture, and its remnants can block blood flow in the vessel. This process deprives the heart of nutrients, and results in death of cardiac tissues, an outcome known as myocardial infarction, or heart attack. Because inflammation is centrally involved in the progression of CHD, studies have examined whether the presence of inflammatory molecules forecasts disease. This work shows that high levels of such molecules, particularly CRP and IL-6, confer risk for later CHD morbidity and mortality (Libby, 2002).

WHERE DO WE GO FROM HERE?

While several of the model's basic predictions have been confirmed, more work needs to be done before its overall utility can be evaluated. The first step in the process should entail testing the model's mediational hypotheses. Do stressful experiences foster

depressive symptoms and cardiac disease by triggering inflammation? Does inflammation operate as a bidirectional pathway linking depression and atherosclerosis? To answer these questions, researchers will need to conduct multiwave prospective investigations assessing constructs frequently. If the model's predictions turn out to be accurate, it will become important to further differentiate its constructs so that their most toxic elements are revealed. Must stressors be severe, like caregiving, to bring about inflammation? Or can more day-to-day concerns such as deadlines and traffic elicit the same processes? There are also nagging questions about the depression construct. Do the symptoms of depression have a unique capacity to initiate the cascades depicted in the model, or is their effect attributable to a broader cluster of negative emotions that also includes anger and anxiety (Suls & Bunde, 2005)? For the model to be maximally valuable as a research tool, the next wave of studies will have to distill these constructs. Fortunately, there are some good leads to guide this work. For example, an intriguing program of research indicates that when stressors elicit feelings of shame, they are especially potent triggers of inflammation and have a special capacity to bring about depressive episodes (Dickerson, Gruenewald, & Kemeny, 2004; Kendler, Hettema, Butera, Gardner, & Prescott, 2003). As time goes on it will also become important to incorporate additional mechanisms linking the model's constructs. Research has already identified a number of candidate pathways. In focusing our discussion on inflammation, we do not mean to imply that these pathways are unimportant; we simply view inflammation as the best candidate for pulling together the disparate literatures we have discussed. Of course, for the model to be complete, these other pathways must be integrated. To the extent that the next wave of studies can meet these challenges, researchers will be able to develop convincing mechanistic explanations for the age-old belief that the mind and body are connected.

Recommended Reading

Irwin, M.R. (2002). Psychoneuroimmunology of depression: Clinical implications. *Brain, Behavior and Immunity*, *16*, 1–16.

Kop, W.J. (1999). Chronic and acute psychological risk factors for clinical manifestations of coronary artery disease. *Psychosomatic Medicine*, *61*, 476–487.

Maier, S.F., & Watkins, L.R. (1998). (See References)

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REFERENCES

Barefoot, J.C., & Schroll, M. (1996). Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation*, *93*, 1976–1980.

Dew, M.A. (1998). Psychiatric disorder in the context of physical illness. In B.P. Dohrenwend (Ed.), *Adversity, stress, and psychopathology* (pp. 177–218). New York: Oxford University Press.

Dickerson, S.S., Gruenewald, T.L., & Kemeny, M.E. (2004). When the social self is threatened: Shame, physiology, and health. *Journal of Personality*, *72*, 1191–1216.

Dong, M., Giles, W.H., Felitti, V.J., Dube, S.R., Williams, J.E., Chapman, D.P., & Anda, R.F. (2004). Insights into causal pathways for ischemic heart disease: Adverse childhood experiences study. *Circulation*, *110*, 1761–1766.

Kendler, K.S., Hettema, J.M., Butera, F., Gardner, C.O., & Prescott, C.A. (2003). Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. *Archives of General Psychiatry*, *60*, 789–796.

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, U.S.A.*, *100*, 9090–9095.

Lesperance, F., Frasure-Smith, N., Talajic, M., & Bourassa, M.G. (2002). Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation*, *105*, 1049–1053.

Libby, P. (2002). Atherosclerosis: The new view. *Scientific American*, *286*, 46–55.

Maier, S.F., & Watkins, L.R. (1998). Cytokines for psychologists: Implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychological Review*, *105*, 83–107.

Maier, S.F., Watkins, L.R., & Nance, D.M. (2001). Multiple routes of action of IL-1 on the nervous system. In R. Ader, D. Felten, & N. Cohen (Eds.), *Psychoneuroimmunology* (3rd ed., pp. 563–579). New York: Academic Press.

Matthews, K., & Gump, B.B. (2002). Chronic work stress and marital dissolution increase risk of posttrial mortality in men from the Multiple Risk Factor Intervention Trial. *Archives of Internal Medicine*, *162*, 309–315.

Miller, G.E., Cohen, S., & Ritchey, A.K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid resistance model. *Health Psychology*, *21*, 531–541.

Miller, G.E., Stetler, C.A., Carney, R.M., Freedland, K.E., & Banks, W.A. (2002). Clinical depression and inflammatory risk markers for coronary heart disease. *The American Journal of Cardiology*, *90*, 1279–1283.

Motivala, S.J., & Irwin, M.R. (in press). Sleep and immunity: Cytokine pathways linking sleep and health outcomes. *Current Directions in Psychological Science*.

Musselman, D.L., Lawson, D.H., Gumnick, J.F., Manatunga, A.K., Penna, S., Goodkin, R.S., Greiner, K., Nemeroff, C.B., & Miller, A.H. (2001). Paroxetine for the prevention of depression induced by high-dose interferon alfa. *New England Journal of Medicine*, *344*, 961–966.

Segerstrom, S.C., & Miller, G.E. (2004). Psychological stress and the immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*, *130*, 601–630.

Suls, J., & Bunde, J. (2005). Anger, anxiety, and depression as risk factors for cardiovascular disease: The problems and implications of overlapping affective dispositions. *Psychological Bulletin*, *131*, 260–300.

Yirmiya, R. (1996). Endotoxin produces a depressive-like episode in rats. *Brain Research*, *711*, 163–174.