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Health Psychology: Developing Biologically Plausible Models Linking the Social World and Physical Health

Gregory Miller,[1] Edith Chen,[1] and Steve W. Cole[2]

[1]Department of Psychology, University of British Columbia, Vancouver, V6T 1Z4, British Columbia; email: gemiller@psych.ubc.ca

[2]Department of Medicine, Division of Hematology-Oncology, UCLA School of Medicine, UCLA AIDS Institute, UCLA Molecular Biology Institute, Jonsson Comprehensive Cancer Center and the Norman Cousins Center at UCLA, University of California, Los Angeles, California 90095

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Abstract

Research over the past several decades has documented psychosocial influences on the development and progression of several major medical illnesses. The field is now increasingly focused on identifying the biological and behavioral mechanisms underlying these effects. This review takes stock of the knowledge accumulated in the biological arena to date and highlights conceptual and methodological approaches that have proven especially productive. It emphasizes the value of a disease-centered approach that "reverse engineers" adverse health outcomes into their specific biological determinants and then identifies psychologically modulated neuroendocrine and immunologic dynamics that modulate those pathological processes at the cellular and molecular levels.

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INTRODUCTION

Over the past several decades, there has been an explosion of interest in the area of health psychology, fueled by mounting evidence that psychological factors have important implications for health. The data from this line of work have been sufficiently compelling that a sizeable number of our biomedical colleagues—who were initially and rightfully skeptical of the idea—now believe that factors such as chronic stress, depression, hostility, and social isolation influence vulnerability to certain diseases (Cohen et al. 2007, Glaser et al. 1999, Kiecolt-Glaser et al. 2002). As consensus opinion has come to support a role of psychosocial factors in influencing physical health, research has increasingly focused on identifying the biological and behavioral mechanisms underlying these effects.

The objectives of this review are to take stock of the knowledge accumulated in the biological arena to date and to highlight conceptual and methodological approaches that have proven especially productive. We organize the review around four lines of work that are critical for identifying psychobiological mechanisms: (*a*) research linking psychosocial factors to disease outcomes, (*b*) research linking psychosocial factors to biological intermediaries, (*c*) research identifying biological chains of causality, and (*d*) research connecting discoveries across these three domains. We take a disease-centered approach that "reverse engineers" adverse health outcomes into their specific biological determinants and then identifies psychologically modulated neuroendocrine and immunologic dynamics that modulate those pathological processes at the cellular and molecular levels. Much of our mediational discussion focuses on the sympathetic nervous system (SNS), the hypothalamic pituitary adrenocortical (HPA) axis, and the immune system. These are certainly not the only potential mediators linking mind and body, but they are the most extensively studied intermediates and influence each of the diseases we consider.

PSYCHOSOCIAL FACTORS AND DISEASE OUTCOMES

The starting point for mechanistic health psychology research should be a robust clinical phenomenon. By this, we mean a well-established association between a psychosocial characteristic and the incidence or progression of a serious medical illness (i.e., changes in experienced symptoms or biological processes that drive disease progression). We say this because

research that simply documents linkages between psychosocial factors and biological parameters that do not have clear implications for health or disease will have limited theoretical utility. For example, many studies have documented relationships between acute stress and transient alterations in the distribution of certain leukocyte subtypes in circulating blood (particularly natural killer cells). However, no evidence indicates that these small variations in leukocyte trafficking have any material health impact. A surer approach for identifying health-relevant psychobiologic interactions is to begin with a particular disease of interest, ask first which biological processes are involved in the development and progression of that disease, and then empirically analyze those processes to determine which are subject to regulation by the social world and the behavioral and biological processes it modulates. For example, dozens of studies now link depressive symptoms with morbidity and mortality from heart disease (see reviews by Rugulies 2002, van Melle et al. 2004, Wulsin & Singal 2003). These data provide a strong rationale for moving forward with studies of depression's association with coagulation, inflammation, and other processes that drive atherosclerosis. Likewise, multiple studies link psychosocial risk factors to HIV-1 disease progression (Cole 2006, Cole et al. 1997, Sloan et al. 2007c). This link provided researchers with a rationale for subsequent analyses of the upstream biological processes that drive clinical disease progression (e.g., viral replication, innate immune responses; Cole et al. 2001, 2003), which ultimately led to the identification of specific molecular mechanisms mediating the effects of stress-induced neuroendocrine dynamics on HIV-1 pathogenesis (Cole et al. 1998, 1999, 2001; Collado-Hidalgo et al. 2006; Sloan et al. 2006, 2007a,b, 2008). Thus, successful discovery of pathways mediating biobehavioral influences on disease depends critically on the availability of a good basic understanding of disease pathogenesis (to guide the bottom-up selection of specific pathophysiologic targets) and the identification of a robust clinical phenomenon (to guide the top-down targeting of specific psychobiologic pathways).

What, then, constitutes a robust clinical phenomenon? Ideally, a relationship between psychosocial risk factors and clinical disease outcomes would be documented in a series of independent prospective epidemiologic studies that are well powered, carefully evaluate potential sources of confounding, and utilize meaningful clinical outcomes such as morbidity and mortality as endpoints. For example, several studies have shown that high levels of chronic stress are associated with subsequent increases in morbidity and mortality from a variety of diseases, including respiratory infection, cardiovascular disease, and HIV/AIDS (see reviews by Cohen et al. 2007, Krantz & McCeney 2002), as well as adverse clinical outcomes such as impaired wound healing (Kiecolt-Glaser et al. 1995, 2005). A number of individual psychological characteristics have also emerged as robust risk factors for some diseases. For example, both hostility and depression have been linked repeatedly with the incidence and progression of cardiovascular disease (see reviews by Miller et al. 1996, Rugulies 2002, Smith 1992, van Melle et al. 2004, Wulsin & Singal 2003). At the broader level of analysis, features of the larger social environment such as low socioeconomic status (SES; see reviews by Adler et al. 1993, Chen et al. 2002, Marmot & Wilkinson 2000) and social isolation (see reviews by Berkman et al. 1979, Berkman & Kawachi 2000, House et al. 1988) have proven to be robust predictors of adverse outcomes in the context of cardiovascular, respiratory, and infectious diseases, as well as certain cancers.

Although these results linking psychosocial factors with medical outcomes are provocative, it is important to remember that they come from observational studies that cannot clearly determine the direction of causality among the variables analyzed. Thus, when embarking on a mechanistic program of research in health psychology, it is often useful to consider whether the linkage of interest might be causally substantiated with other

methodologies. For ethical reasons, human subjects cannot be randomly assigned to most of the psychosocial circumstances of interest in health psychology. However, they can be randomly assigned to interventions that alter the psychosocial or biomedical consequences of those circumstances. To the extent that such interventions are successful at influencing biomedical endpoints, they provide convincing evidence that a psychosocial characteristic is acting on disease in a causal fashion. For example, in a classic intervention trial, coronary heart disease (CHD) patients were randomized to rehabilitation programs with or without counseling for the behavior pattern known as Type A. Patients who received the counseling not only showed declines in Type A behaviors, but were significantly less likely to have a recurrent myocardial infarction over follow-up (Friedman et al. 1986). In a more recent trial of patients with ischemic heart disease, routine medical care was delivered with or without stress management. Afterward, patients who received stress management showed better endothelial function and fewer wall motion abnormalities than the patients who did not receive stress management (Blumenthal et al. 2005).

Unfortunately, only a handful of trials targeting psychosocial parameters have reported positive clinical outcomes. Notably, a recent large multisite trial aimed at alleviating low social support and depression in cardiac patients found no effects of intervention on mortality across the whole sample (Berkman et al. 2003). A critical review of the literature on psychosocial interventions for cancer patients also found little evidence that such treatments reduce morbidity or mortality (Coyne et al. 2007). Null findings such as these do not exclude the possibility of a causal influence for psychosocial circumstances, as there may be many other reasons why a psychosocial intervention would fail to influence morbidity or mortality (e.g., poor measurement, insufficient statistical power, weak adherence to the intervention, or weakness in the intervention's ability to significantly impact the behavioral risk factor or the key pathophysiologic process in the disease; Carney et al. 1999, Coyne et al. 2007, Miller & Cohen 2001). However, when negative findings emerge from intervention trials, it implies that the mechanistic researcher needs to look to other approaches to substantiate the epidemiologic phenomenon s/he is trying to unpack.

Animal models can often provide good mechanistic evidence relating psychosocial risk factors to physical health. Unlike humans, animals can be randomly assigned to psychologically difficult circumstances and monitored over time to determine whether these experiences influence disease outcomes. Many studies of this nature have been performed and, encouragingly, their findings often converge with correlational evidence from human epidemiologic research. Some notable examples include the results linking long-term stress with vulnerability to respiratory infection, CHD, and accelerated progression of HIV/AIDS, as well as data linking subordinate social status to greater morbidity and mortality (see reviews by Bailey et al. 2007, Manuck et al. 1995, Sloan et al. 2007c, Verrier & Lown 1984). Not all psychosocial circumstances can be accurately modeled in animals, but mechanistic research can operate on firmer ground when animal models are available to establish causal relationships and access biological tissues for mechanistic analyses.

PSYCHOSOCIAL FACTORS AND BIOLOGICAL INTERMEDIARIES

Once a robust linkage between a psychosocial factor and a clinical health outcome has been identified, the next step is to determine what biological processes convey those effects into the physical environment of disease pathogenesis (i.e., what biological mediators carry psychosocial influences "under the skin"). Significant progress has been made in understanding the biological correlates of stress, depression, social support, and SES. These data provide new substantive insights and establish a conceptual approach for future studies mapping relationships between extraindividual social risk factors

and their intraindividual impact on physiology and disease.

Psychological Stress

Decades of research have catalogued the endocrine and immune changes that result from stressful experience. Early studies identified general relationships between differing psychological states (e.g., relaxed vegetative states versus acute stress–active coping responses versus more severe overwhelming threat) and distinct patterns of neuroendocrine response (e.g., parasympathetic nervous system activity, SNS activity, and HPA activation, respectively; reviewed in Weiner 1992). Recent studies have clarified the psychological antecedents that drive human neuroendocrine responses. An influential meta-analysis by Dickerson & Kemeny (2004) indicates that human cortisol responses to acute laboratory stressors are most pronounced in situations that pose a social threat to the individual. Increased secretion of cortisol is also seen in persons facing real-life stressors that are more chronic in nature. However, meta-analysis also shows that these dynamics shift as time passes (Miller et al. 2007). Early in the course of a chronic stressor, there is robust activation of the HPA axis, which results in elevated concentrations of adrenocorticotrophic hormone and cortisol. As time passes, HPA axis activity diminishes, and cortisol secretion rebounds to normal and later to below normal. Recent theoretical analyses have also linked differential profiles of autonomic nervous system response to distinct psychological appraisals of a stressful situation (e.g., threat versus challenge; Tomaka et al. 1997). As with the HPA axis, data increasingly suggest that social threat or uncertainty may be a particularly powerful determinant of SNS activity (Cole et al. 2003, Kagan 1994). Thus, many of the physiologic and health dynamics that were once construed as driven by stress are increasingly being analyzed in terms of the social etiology of individual neuroendocrine activity. This provides a conceptual bridge between epidemiologic data that emphasize socioenvironmental risk factors in health at the population level and traditional intraindividual analyses of stress effects on physiology.

Three decades of research in psychoneuroimmunology (PNI) have also identified distinct immunobiological correlates of differing psychological states. A meta-analysis of human PNI studies found that the chronicity and severity of stressors played a key role in moderating the nature and intensity of associated alterations in immunologic parameters (Segerstrom & Miller 2004). Acute stresses such as public speaking amplify several features of the innate immune response (e.g., natural killer cell trafficking and cytotoxicity). These effects are transient and may represent an immunologic component of the broader fight-or-flight response to threat. Stressors that persist for longer durations, such as school exams, are associated with alterations in adaptive immune responses (e.g., humoral immune responses mediated by B-lymphocytes versus cellular immune responses mediated by cytotoxic T-lymphocytes). Several studies suggest that antibody-mediated humoral immune responses can be enhanced by chronic stress, whereas some aspects of cell-mediated response are suppressed. Stressors that are both severe and stable, such as serving as a caregiver for a demented relative, often impair multiple aspects of the immune response. For example, relative to age-matched controls, caregivers produce fewer virus-specific antibodies following influenza vaccination, show delayed healing of experimentally administered wounds, and show down-regulation of several immunobiological processes in ex vivo assays of leukocyte function (e.g., Kiecolt-Glaser et al. 1991, 1995, 1996; Vedhara et al. 1999). However, research increasingly shows that stress is not globally immunosuppressive. Whereas chronic stress can suppress several aspects of adaptive immune function, it also appears to induce a chronic and systemic state of mild inflammation (Kiecolt-Glaser et al. 2003, Miller et al. 2008, Ranjit et al. 2007a). This is manifest by increased circulating concentrations of the inflammatory biomarkers C-reactive protein (CRP) and interleukin-6 (IL-6). Because

inflammation is a key pathogenic mechanism in many infectious, cardiovascular, and neoplastic diseases (Coussens & Werb 2002, Eccles 2005, Libby & Theroux 2005, Perkins 2007), stress enhancement of inflammatory signaling has provided a new set of mechanistic hypotheses for understanding the pathways that link psychosocial characteristics with morbidity and mortality (also see Kiecolt-Glaser et al. 2002).

Depression

Severe depression is often associated with increased circulating levels of HPA and SNS neuroendocrine mediators (see reviews by Musselman et al. 1998, Plotsky et al. 1995). About half of patients with severe forms of depression also show dysregulation of the negative-feedback circuit that regulates HPA output (Haskett 1993). However, these patterns of excess HPA and SNS activity are seldom found in patients with milder versions of depression (Anisman et al. 1999, Miller et al. 1999, Ravindran et al. 1995, Stetler et al. 2004, Strickland et al. 2002).

Depressed individuals also show patterns of immune alteration similar to those observed in chronic stress; e.g., impairments in some cellular immune parameters, delayed healing of experimentally administered wounds, and blunted antibody responses to vaccination, accompanied by increased systemic inflammatory activity (e.g., Bosch et al. 2007; Glaser et al. 2003; Irwin et al. 1998; Kop et al. 2002; Lesperance et al. 2004; Miller et al. 2002b, 2005; see reviews by Irwin 2001, 2002; Raison et al. 2006). Similar patterns are seen in both clinically depressed patients and those with high levels of dysphoric affect. The linkage between depressive symptoms and systemic inflammation has been of special interest to researchers lately because it may help to explain the excess cardiovascular morbidity and mortality associated with depression. Inflammation is a key pathologic mechanism underlying heart disease, and elevated levels of biomarkers such as CRP and IL-6 forecast clinical events such as myocardial infarction and coronary death (see review by Libby & Theroux 2005).

Social Support

Some data suggest that people who are socially isolated show higher circulating levels of cortisol, epinephrine, and norepinephrine (see reviews by Seeman & McEwen 1996, Uchino et al. 1996), although other studies find no substantial differences (e.g., Cole 2008, Cole et al. 2007). However, recent data suggest that alterations in glucocorticoid receptor (GR) signaling associated with subjective social isolation may result in impaired physiologic control of inflammation by the HPA axis, despite normal circulating cortisol levels (e.g., Cole 2008, Cole et al. 2007). These alterations in hormonal receptor sensitivity result in altered gene expression profiles in immune cells (Cole et al. 2007), which could potentially explain why socially isolated people also show weaker antibody responses, and greater vulnerability to respiratory infection following exposure to a virus (e.g., Cohen et al. 1997, Pressman et al. 2005; see review by Cohen 2004). Data from experimental primate models also show that stressful social relationships can exacerbate viral infections by altering SNS neural regulation of the lymphoid organs in which leukocytes generate antiviral responses, resulting in suboptimal gene expression responses to infection (Sloan et al. 2007b). Consistent with these alterations in immune cell sensitivity to regulation by the HPA axis and SNS, people with low social support also show elevated circulating levels of C-reactive protein and interleukin-6 (Loucks et al. 2006a,b). Most of these physiological correlates of the social world are evident in persons who report feeling lonely on a chronic basis, irrespective of their objective social conditions (e.g., Adam et al. 2006, Cole et al. 2007, Pressman et al. 2005; see reviews by Hawkley & Cacioppo 2007, Kiecolt-Glaser 1999).

Socioeconomic Status

Several studies have also linked low socioeconomic status to higher levels of cortisol and epinephrine during daily life (Cohen et al. 2006a,b; Evans & English 2002; Janicki-Deverts et al. 2007; Lupien et al. 2000, 2001)

as well as to increased circulating concentrations of inflammatory biomarkers for CHD such as CRP and IL-6 (Hemingway et al. 2003, Panagiotakos et al. 2005; see review by Chen & Miller 2007a).

CONCEPTUALIZING LINKS BETWEEN THE SOCIAL WORLD AND BIOLOGY

In many cases, the starting point phenomenon for the above studies is a link between an individual-level psychosocial characteristic (e.g., chronic stress) and a specific clinical outcome (e.g., respiratory infection). As researchers develop more complete psychobiological theories of disease, it is important to create rich and comprehensive models of the social context of disease by considering factors at multiple social levels (e.g., individual, peer, community, culture). For researchers starting with distal social environment factors such as SES, the challenge is to uncover the more proximal psychosocial mechanisms that bring the larger social environment down to the level of the individual. For researchers starting with individual psychological characteristics such as stress, the challenge is to gain a richer understanding of the broader social forces that contribute to stress by studying factors beyond the individual level. These more integrative approaches provide a broader understanding of the social context of disease as well as novel insights into developmental structure and even potential interventions targeting specific psychosocial risk factors.

Early-Life Environments and Health

Findings from a number of studies suggest that early-life social environments can have long-lasting impacts on health that persist well into adulthood (see reviews by Barker 1997, Hertzman 1999, Repetti et al. 2002). These findings have been substantiated in experimental research in animal models (see Coe & Lubach 2005, Hodgson & Coe 2005, Meaney & Szyf 2005). One psychosocial model explaining this phenomenon implicates exposure to risky family environments early in life (Repetti et al. 2002). Risky families are cold, have high levels of conflict and aggression, and rarely undertake nurturing behaviors. The model states that these types of families engage in more harsh, inconsistent parenting, which in turn leads children to have greater difficulty regulating their emotions. As a result, biological stress response systems become dysregulated, leading to risk for a variety of health problems over time (Repetti et al. 2002). Recently, empirical evidence has begun to emerge for a psychosocial model linking early-life environments to adult biological profiles. For example, young adults who reported more difficult family environments in childhood had higher levels of current negative emotions such as depression and anxiety, which in turn were associated with higher basal levels of cortisol (Taylor et al. 2004). Similarly, adults who reported difficult early-life family environments had higher current levels of depression and less mastery, which in turn were associated with greater elevations in the inflammatory marker CRP (Taylor et al. 2006). These findings suggest pathways by which the broader social context (early family environment) may shape the development of individual characteristics (negative emotions), which in turn have implications for individual hormonal and immune profiles.

Socioeconomic Status and Health

Psychosocial factors are also thought to play an important role in the relationship between SES and health (Marmot & Wilkinson 2000), with stress being one commonly implicated pathway. Low-SES individuals experience greater numbers of stressful life events (Brady & Matthews 2002), and greater stress has been found to partially explain relationships between low SES and poor self-reported health (Cohen et al. 1999). However, in seeking to understand how larger social forces such as SES and external stimuli such as negative life events might have biological effects, a theory is needed to explain how these factors operate at the individual level.

Our research group has proposed that external social environments have to be perceived by the individual in negative ways in order to have detrimental biological effects (Chen & Miller 2007b). In particular, we postulate that children who grow up in low-SES neighborhoods are more likely to experience negative life events, especially ones that are unpredictable. As a result, low-SES children will be more likely to develop a sense of vigilance and a lowered threshold for perceiving threat in new situations. In life situations that are ambiguous (where the outcome and intention of another person are unclear), we argue that differences between low- and high-SES children will be most pronounced, and that low-SES children will interpret these situations in a much more threatening manner than high-SES children. In turn, these types of threat interpretations are hypothesized to affect biological responses.

Empirically, we tested this theory by devising a set of videos depicting different types of life situations. Children and adolescents watched these videos and were interviewed about their interpretations. Through this approach, we were able to hold the exposure (the situation) constant and assess variability in interpretations. We found that low SES was associated with greater interpretations of threat during ambiguous, but not negative, social situations (Chen & Matthews 2003). We further documented that threat interpretations during ambiguous social situations statistically mediated the relationship between low SES and heightened cardiovascular reactivity in healthy adolescents, and heightened inflammatory profiles in children with asthma (Chen et al. 2004, 2006). These findings suggest that the larger social environment is able to affect biological responses in an individual via the ways they perceive their social environment.

Social Context of Emotions

The above studies provide examples of how to connect larger social factors such as SES to individual processes. However, many researchers interested in mechanisms have an individual psychosocial characteristic such as stress or depression as their starting point. In these cases, a more comprehensive model would also seek to understand the broader context that underlies the development of these individual characteristics. One example of this approach is the proposal by Dickerson & Kemeny (2004) that the social evaluative nature of a threat—the extent to which a person could potentially be judged negatively by others—plays a significant role in determining the intensity of cortisol response to a fixed challenge (the Trier Social Stress Test). In their theory, the subjective experience of shame represents a key psychological driver of the stress response and thereby serves as a portal between external conditions and the biology of the body. Extending this approach to an evolutionary context, Dickerson and Kemeny theorized that just as humans have evolved a physical response system designed to protect the self from harm, by eliciting emotions (e.g., fear) and biological responses (e.g., fight-or-flight response) in the face of danger, they have also evolved a parallel social self-preservation system that mobilizes emotions (e.g., shame) and biological responses (cortisol secretion and systemic inflammation) in the face of threats to one's social standing within a group (Dickerson et al. 2004).

Empirical evidence is beginning to emerge in support of this theory. When participants were asked to undergo an acute laboratory stressor either in the presence of an audience (social evaluation) or alone (no social evaluation), the audience condition elicited more shame and greater cortisol responses compared to doing the same task alone (Gruenewald et al. 2004). In a study of competitive ballroom dancers, cortisol levels increased on competition days but not on training days in which identical routines were performed (but without evaluation by judges). Furthermore, cortisol increases were greater during competition for couples dancers (where each individual had a greater focus of evaluation from judges and audience members) compared to group dancers (Rohleder et al. 2007). Collectively, this line of work provides an intriguing example of

building a broader theoretical model around empirical evidence tying a context (social evaluation by others) to a specific individually experienced emotion (shame) and in turn to specific biological responses (cortisol output).

DEVELOPING A CAUSAL BIOLOGICAL CHAIN FOR PSYCHOSOCIAL FACTORS

Much of the existing mechanistic research in health psychology relates a single psychosocial characteristic (e.g., depression) to a single presumptive biological mediator (e.g., cortisol) or to a small group of conceptually related mediators (e.g., IL1-β and IL-6). Although this approach has proven useful, we argue that the field now must move beyond assessments of solitary biomarkers toward more sophisticated causal models of how psychosocial factors come to influence the course of disease.

In order to proceed on a theoretically informed search for mechanisms, one must understand the biological processes that drive initiation and progression of a specific disease. Hence, one approach to developing comprehensive biological models is to map out the pathophysiology of the disease and then identify specific elements of that system that might be regulated by proposed biobehavioral mediators (e.g., the HPA axis or SNS). Research utilizing this approach could then proceed in a systematic explanatory progression, whereby one would (*a*) identify the most proximal biological pathways linked to clinical disease outcomes (i.e., mechanism of pathogenesis), (*b*) test whether the psychosocial factor of interest is associated with these proximal biological mechanisms, and then (*c*) identify the biobehavioral mediators that regulate these proximal biological mechanisms. One could then test whether the psychosocial factor of interest is associated with these regulatory mechanisms in standard correlational mediation analyses or, ideally, manipulate putative mediators and observe alterations in the basic relationship between psychosocial factors and disease-proximal biology. In this way, researchers can begin to build a systematic and convincing argument about the causal chain of biological relationships that underlie the link between a social factor and a clinical health outcome.

Stress and Asthma

We provide one example of this type of approach based on our work in childhood asthma. Psychological stress has been linked to poorer clinical asthma outcomes, such as an increased risk of asthma exacerbations (Sandberg et al. 2000, 2004). Asthma is an inflammatory disease, wherein activation of eosinophils, production of immunoglobulin E, and degranulation of mast cells form key events leading to the release of allergic mediators such as histamines and leukotrienes. These molecules bring about edema, smooth muscle constriction, and mucus production in the airways, resulting in clinical symptoms such as wheezing, chest tightness, and shortness of breath. Based on these working biological models, we tested whether psychological stress would be associated with the above types of inflammatory markers in children who had been physician-diagnosed with asthma. Children were interviewed about life stress, and peripheral blood samples were collected to measure eosinophils. We documented that children with asthma who experienced higher levels of chronic home-life stress had greater eosinophil counts, even after controlling for a variety of medical and demographic characteristics (Chen et al. 2006). This study provided a biological starting point (increased eosinophil counts) for understanding why psychological stress would be linked to clinical outcomes such as increased asthma exacerbations.

We then asked what immune processes might foster the production and activation of eosinophils. It turns out that certain cytokines—primarily IL-5—are responsible for activating eosinophils and recruiting them to the airways. Because cytokines are only released when immune cells are activated, we set up a laboratory model for activating immune cells in vitro, and we tested whether stress would be associated with the production of IL-5 after

participants' mononuclear cells were stimulated with a mitogen. We found that higher levels of chronic home stress were also associated with greater stimulated production of IL-5 (Chen et al. 2006). This finding suggests that given an equivalent exposure to asthma-inducing allergens, children with asthma who are experiencing stress will exhibit heightened inflammatory responses compared to children with asthma who are under low stress. This now provided us with a second piece of evidence of a social factor (stress) linked with biological processes (increase in both stimulated cytokine production and eosinophil counts), and in a direction that is consistent with the clinical evidence of greater risk for asthma morbidity.

From there, we went one step deeper and asked what cellular processes might regulate inflammatory responses such as cytokine production. Immune cells are equipped with mechanisms to both activate and terminate inflammatory responses. Hormones such as cortisol are known to provide anti-inflammatory signals to immune cells. Because stress is known to activate the HPA as well as the SNS, we hypothesized that under conditions of chronic stress, persistent elevations in the hormonal products of these axes (cortisol, epinephrine, and norepinephrine) would result in a compensatory down-regulation of the receptors for these hormones—for example, the GR as well as the β2 adrenergic receptor (β2AR). As a result, the immune system's ability to respond to anti-inflammatory signals from these hormones would be reduced, and inflammatory processes would flourish (Miller et al. 2002a). In a sample of children with asthma, we tested whether life stress was associated with the expression of messenger RNA (mRNA) for the GR and β2AR. We found that children with asthma who simultaneously experienced high levels of both acute and chronic stress exhibited a 5.5-fold reduction in GR mRNA and a 9.5-fold reduction in β2AR mRNA relative to children with asthma without comparable stressor exposure (Miller & Chen 2006). This diminished expression of the GR and β2AR genes suggests that children with asthma who are experiencing acute and chronic stress may be both more vulnerable to inflammation and less responsive to asthma medications (such as inhaled corticosteroids and beta-agonists, which act through these receptors). Overall, these patterns suggest that even molecular pathways involved in the regulation of inflammation are patterned by psychological stress in children with asthma and hence may help explain biologically why children under stress would experience poorer asthma outcomes.

Stress and Cortisol

Another approach to developing comprehensive biological models is to start with a well-defined psychobiological effect and then systematically explore its implications at the level of tissues and organs. For example, there are well-documented relationships between a variety of psychosocial characteristics we discuss and the output of cortisol (see reviews by Dickerson & Kemeny 2004, Haskett 1993, Miller et al. 2007). However, circulating cortisol is only the starting point for a complex and tightly regulated chain of events and by itself does not explain the differential disease risk attributed to these characteristics. Instead, the consequences of cortisol's action on the behavior of disease-related cells constitute a mechanism of disease. A long chain of events is required to translate alterations in circulating cortisol levels into differential disease risk. Once it is released, cortisol must bind to GRs or mineralocorticoid receptors (MRs) located in the cytosol of a cell. The newly formed receptor-hormone complex must then translocate to the nucleus, where it can modify the gene expression routines that govern cellular behavior.

Most tissues are equipped with a host of counterregulatory mechanisms that can potentially intervene in this process to insure that acute changes in cortisol do not drastically disrupt homeostasis. This means that even if cortisol levels are increased markedly by a psychosocial circumstance, the bodily tissues this hormone regulates may not be affected commensurately because counterregulatory

mechanisms may alter how loudly cortisol's signals are heard. One way in which tissues undertake counterregulatory actions is by altering characteristics of the receptors to which cortisol binds. To counterbalance the fact that cortisol levels have increased, cells can reduce the density or activity of their GRs and MRs. Receptors that are downregulated or desensitized will pass on fewer of cortisol's signals to the nucleus of the cell, where the gene expression routines that govern cellular behavior are carried out (Cole et al. 2007).

To evaluate how these dynamics play out with regard to psychosocial characteristics, some researchers have begun studying how bodily tissues respond to bursts of cortisol (see Ebrecht et al. 2000, Rohleder et al. 2001). For research focused on the immune system, this can be done by collecting white blood cells, stimulating them with bacterial products, and then adding a dose of cortisol to the culture. Because cortisol has powerful anti-inflammatory properties, its presence should dampen the cellular response to bacterial stimulation. If it does not, one can infer that the system has lost an important regulatory constraint. Some research suggests that this may occur with stress. For example, one study found that among people facing a severe chronic stressor—being the parent of a child with cancer—white blood cells' sensitivity to inhibition by dexamethasone was reduced (Miller et al. 2002a). This was manifest by a reduction in the ability of dexamethasone to suppress bacterially stimulated production of IL-6, a molecule that plays a key role in organizing inflammatory responses. Together, these findings suggest that psychological circumstances not only modify hormonal outputs, such as cortisol levels, but also modify the way the immune system responds to signals from cortisol. In turn, these responses to cortisol will influence the ability of certain genes to get activated and engage in protein synthesis.

The cortisol challenge paradigms outlined above measure the capacity of an immune cell to respond to a hormonal stimulus in vitro, but they do not tell us how such dynamics are actually playing out under physiologic conditions. The latter has been a challenging question to answer, but recent developments in functional genomics and bioinformatics have provided new methodologies for gauging the steady-state regulatory actions of hormones such as cortisol. One approach uses microarray technology to monitor the activity of all ~22,000 human genes in a tissue of interest (e.g., immune cells collected from peripheral blood). This analysis reveals a subset of genes that are differentially expressed by two groups of patients, e.g., those who have and have not been exposed to some psychosocial circumstance of interest. Bioinformatics technology is then used to discern what these genes have in common. This can be done by scanning the upstream regulatory DNA sequences (promoter regions) of differentially expressed genes to determine the prevalence of DNA motifs that serve as targets for hormone- and cytokine-activated transcription factors (Cole et al. 2005). With these data in hand, one can make reverse-inferences about how active certain signaling pathways have been in vivo. For example, if the genes that tend to be overexpressed in one set of patients show a disproportionate prevalence of transcription factor-binding motifs for the GR, one can infer that their tissue has been exposed to greater cortisol-mediated signaling. These methods enable researchers to quantify how loudly cortisol signals are being heard by the genome and what effect this is having on the ability of genes to get switched on to initiate protein synthesis. Because this approach measures postreceptor gene transcription, it integrates the effect of differential HPA axis output (e.g., bioavailable cortisol) and differential GR-mediated signal transduction.

Our team recently used this strategy to evaluate how a severe chronic stressor—caring for a family member with brain cancer—influenced cortisol-mediated signaling in the white blood cells that drive inflammation (monocytes). This analysis revealed that stressed patients had diminished expression of genes bearing response elements for GR and at the same time heightened expression of transcripts with response elements for proinflammatory transcription

factors such as nuclear factor κ-B (Miller et al. 2008). In other words, these data showed that caregivers' monocytes were registering fewer cortisol signals than were monocytes of controls. As a result, genes that cortisol usually switches on were not being expressed as strongly in monocytes from caregivers as those from controls, and genes that cortisol usually silences were more active in caregivers than in controls. This in vivo readout suggests an intriguing scenario for how chronic stressors influence disease: By interfering with the ability of cortisol to deliver signals to white blood cells, stressors may facilitate the kinds of proinflammatory gene expression cascades that contribute to coronary disease, autoimmune disorders, and infectious diseases (also see Miller et al. 2002a, Raison & Miller 2003).

By targeting multiple levels of analysis in the biological domain, researchers also gain an important advantage of being able to uncover patterns that may have been missed by focusing on only one level of biological mechanisms. For example, in the above study, we collected daily saliva samples from participants, but chronic stress was not associated with differential cortisol levels. Similarly, we measured the expression of GR in white blood cells, but this too was unrelated to chronic stress. If we had constrained our analysis to include only hormonal outputs or receptor expression, we would have mistakenly concluded that cortisol, and the tissues it regulates, are unaffected by caregiving. But as the gene expression profile revealed, this was not the case. Instead, we were able to discover that the monocytes of chronically stressed individuals are not hearing cortisol signals from the body as loudly as they should, even though this hormone is being secreted in sufficient quantities and sufficient numbers of receptors are available to bind it. As a consequence of that alteration, proinflammatory genes were overexpressed, leading to a change in circulating indicators of inflammation (e.g., CRP).

One criticism sometimes leveled at microarrays is based on the assumption that they inherently involve nonhypothesis-driven exploratory analyses. However, the application we describe above shows how microarrays can be used to test a priori mechanistic hypotheses (i.e., that stress-induced alterations in inflammation are mediated by desensitization of the GR-mediated gene transcription control pathway). Of course, microarray technology can also be used for "unbiased discovery" studies to reveal patterns in the data that an investigator may have otherwise overlooked. We believe that hypothesis-free discovery-based approaches can be quite useful, especially in areas where there is little pre-existing biological theory to guide research, and only a fraction of the potential mechanisms have been seriously explored. Theory-driven research is of course preferable in cases where strong theories exist. In that sense, microarrays as a technology are much like any other tool (e.g., an inferential statistical test or a CRP assay)—their epistemological strength derives from the research context in which they are used (e.g., in experimental studies or hypothesis-driven observational analyses) and is not a property of the methodology per se.

PUTTING IT ALL TOGETHER

Ultimately, the most convincing mechanistic programs of research methodically piece together both the psychosocial and biological sides in a way that paints a detailed picture of the linear progression from social environment to disease outcome. As research moves deeper into the pathophysiology of a disease, it should continue to test whether the target psychosocial factor remains associated with each step in the disease process, in order to identify the biological pathways that are the most plausibly influenced by the social world. In addition, as the work moves across different levels on the psychosocial end, it should continue to test whether each level (e.g., cultural influences, community influences, family factors, and individual characteristics) remains associated with biological processes that contribute to disease outcomes. In this way, research can start broadly on the social end (e.g., with a construct such as SES) and broadly on the clinical end (e.g., with

an outcome like mortality), and systematically establish the links in between that bring the social world and the clinical endpoints closer together. The ultimate goal is to lay out a step-by-step mechanistic model of how the larger social environment gets embedded within an individual and comes to alter biological processes that influence the course of disease. **Figure 1** provides examples of how such models might look, both generally and in the context of specific conditions such as heart disease, asthma, and HIV/AIDS.

We now provide two examples of research that have sought to connect mechanisms at multiple levels along a model of psychological factors to biological processes to disease outcomes. Both investigate the immunologic basis for the link between stress and viral infection—perhaps the best established of all psychoneuroimmunologic phenomena. The first example involves the role of stress in increasing vulnerability to the common cold. High levels of stress have been found to predict increased risk of developing respiratory infections following exposure to various viruses (Cohen et al. 1991, 1998). Production of the proinflammatory cytokine IL-6 is thought to be a key contributor to this process because increases in the concentration of this cytokine precede the development of and correlate strongly with clinical respiratory symptoms. Hence, researchers tested whether psychological stress might activate the production of IL-6, in turn leading to illness symptoms (Cohen et al. 1999). Healthy participants were quarantined, exposed to a respiratory virus, and symptoms and mucus production were monitored over the following week. Higher levels of perceived stress were associated with higher levels of IL-6 during the week following viral exposure. In turn, higher levels of IL-6 were associated with greater symptoms and mucus production. Finally, when the effects of IL-6 were partialled out statistically, the relationship between stress and clinical symptoms/mucus weight dropped by 58% to 67%, suggesting that one biological effect of stress is to heighten inflammatory responses to viral exposure, which in turn increase respiratory infection symptoms (Cohen et al. 1999).

A second example involves the relationship between stress and accelerated progression of HIV-1 infection. This line of research emerged from early epidemiologic observations showing that gay men who concealed their homosexual identity from others showed more rapid progression of HIV-1 infection, including accelerated declines in CD4+ T lymphocyte levels, shorter times to onset of AIDS-defining clinical conditions, and shorter times to death (Cole et al. 1996). Subsequent analyses unpacked the risk factor of "closeting" into its internal psychological motivation—individual differences in sensitivity to social threat (Cole 2006, Cole et al. 1997). That specific intrapsychic translation allowed the generation of hypotheses regarding the biobehavioral mediators involved through analogy to previous research linking social threat sensitivity to individual differences in SNS activity (Kagan 1994). Based on those hypotheses, laboratory studies probed the relationships between closeted social behavior, psychological sensitivity to social threat, increased SNS activity, and the biological process that fundamentally drives HIV-1 disease progression—the rate of viral replication. Findings showed that as much as 90% of the total association between social threat sensitivity and HIV-1 replication could potentially be explained by intervening differences in SNS activity (Cole et al. 2003). To evaluate the plausibility of this relationship from a molecular virologic standpoint, subsequent laboratory studies explored the capacity of the SNS neurotransmitter norepinephrine to enhance HIV-1 replication in cellular model systems (Cole et al. 1998). Those studies identified several molecular mechanisms by which norepinephrine could accelerate viral replication, including increased T cell vulnerability to infection (Cole et al. 1999), increased transcription of the HIV-1 genome (Cole et al. 2001), and decreased antiviral response by host cell cytokines (Cole et al. 1998, Collado-Hidalgo et al. 2006).

Together, those observations utilized an array of different analytic systems to document a chain of binary mechanistic relationships from an observable behavioral risk factor (closeting) to a measurable intrapsychic response (perceived social threat) that activated a known biobehavioral signaling pathway (the SNS/norepinephrine system), which was shown to enhance activity of the key pathogenetic processes known to drive differential risk of disease (HIV-1 replication, antiviral response). Initiating this chain was a cultural context in which homosexual social identity constituted a potential basis for social rejection and consequent subjective threat (Cole 2006). In its system of individual binary relationships, this mechanistic hypothesis was plausible and not particularly complicated. Nevertheless, it still involved more levels of analysis than could be studied tractably in a human research setting (cultural attitudes, individual psychological responses, neural signaling pathways, and the molecular biology of viral replication). To assess the simultaneous plausibility of the system as a whole, the researchers turned to a socially manipulable and tissue-accessible experimental animal model of social threat effects on replication of the Simian immunodeficiency virus (SIV; a close analogue of HIV-1 that infects rhesus macaques). Analyses of animals experimentally infected with SIV and randomly assigned to chronically threatening social conditions versus less stressful stable social conditions showed that social stress did indeed simultaneously increase SNS regulation of immune cells, undermine expression of antiviral cytokines, and accelerate replication of SIV (Sloan et al. 2006, 2007b, 2008). Additional analyses showed that constitutional individual differences in sensitivity to social threat were also associated with increased SNS regulation of the lymph node tissues in which immune responses are initiated (Sloan et al. 2007a). Thus, experimental model systems and naturally occurring analogues of the original socioepidemiologic relationship both support the overarching hypothesis that relationships between social behavior and HIV-1 disease progression are mediated by psychological threat responses that increase SNS signaling to the immune system and thereby alter leukocyte gene expression in ways that facilitate viral replication and accelerate the progression of clinical disease. In this case, refinement of the sociobehavioral risk factor into a psychological process with identifiable neurobiological correlates played a crucial role in developing a plausible mechanistic theory, and its subsequent validation required convergent testing through a variety of methodological approaches (social epidemiology, observational human clinical studies, experimental animal models, and cellular model systems) and across diverse levels of analysis (social, personal, neuroendocrine, cellular, and molecular). This is one of the most ambitious PNI analyses to date, and its empirical success underscores our confidence that complex health psychology phenomena can be successfully analyzed using the simultaneous top-down and bottom-up strategic approach outlined above.

DEALING WITH TEMPORAL DYNAMICS

Analytic models in health psychology often (and usually implicitly) assume that psychosocial characteristics are static and therefore can be measured at any time, and as well, that disease-relevant biological processes will be evident at any point that they are measured. Although this is a reasonable starting point for researchers seeking to clarify the relevant psychosocial and biological processes to include in a model, a full account of health psychology dynamics requires insight into how these relationships originally emerged and how they evolve and change over time.

Connecting the Time Frame of Psychological Constructs to Disease Processes

Psychosocial factors can range in time from those that are briefly experienced to those that

persist for years. Short-lived psychosocial factors typically have a clear onset and offset, and might last anywhere from seconds to several days (e.g., a near-miss traffic accident; failing an exam). Longer-lasting psychosocial factors might persist for months to years, with no clear end. This could include exposures to chronic stress (repeated conflict in the family) or stable characteristics of an individual, such as personality. Similarly, biological mechanisms also may be short acting or long acting. As with psychosocial factors, short-acting biological mechanisms typically have a clear onset and offset and last from seconds to hours (e.g., sympathetic nervous system activation). In contrast, long-lasting biological mechanisms might develop and persist over the course of years (e.g., blood pressure levels). Diseases also often have both acute and chronic manifestations. For example, in asthma patients, exposure to allergic triggers often elicits a short-lived early-phase response that causes bronchial chest tightening and a more chronic late-phase response that leads to persistent airway inflammation. Similarly, heart disease results from atherosclerotic plaques that grow over a period of decades, whereas heart attacks occur when these plaques abruptly burst, causing the formation of thrombi that occlude the heart's blood supply.

Because of these temporal dynamics, mechanistic research programs are most likely to be most successful when their predictors, mediators, and outcomes operate along similar timelines. This perspective is evident, for example, in Kop's model of psychosocial contributions to CHD (Kop & Cohen 2001, 2007). This model classifies the major psychosocial risk factors for CHD according to their duration of exposure (acute versus episodic versus chronic) and temporal proximity to clinical outcomes (hours versus years versus decades). It goes on to propose that each kind of psychosocial circumstance operates through a different underlying biological mechanism to accentuate vulnerability to a different pathological component of CHD. For example, chronic psychosocial factors such as hostility are thought to foster hypertension, sympathetic activation, and lipid abnormalities, which in turn accelerate the earlier and middle stages of the atherosclerosis. Episodic factors such as depression are thought to increase coagulation and inflammation, and by doing so destabilize plaque in patients in the later phases of disease. Finally, acute risks like outbursts of anger are thought to precipitate the transition from asymptomatic atherosclerosis to clinically manifest CHD. By increasing activity of the autonomic nervous system and compromising myocardial oxygen supply, these brief events foster plaque rupture, ventricular arrhythmia, and other clinical phenomena. Although decisive empirical evidence for these distinctions is still required, this model provides a promising integrative approach because it focuses attention on the natural history of the disease, suggests places where psychosocial circumstances are likely to intersect with it, and proposes mediators that are biologically and temporally plausible.

Understanding the Temporal Dynamics of Psychobiological Effects

Some have argued that psychosocial factors may not always have immediate, observable effects on biology and health, but rather that there may be critical time periods in life when the biological effects of a psychosocial factor are most likely to occur (e.g., Coe & Lubach 2003). For example, there is mounting evidence that unfavorable socioeconomic circumstances in the early years of life are associated with increased vulnerability to various diseases in adulthood (Cohen et al. 2004, Kittleson et al. 2006, Lawlor et al. 2006; see review by Galobardes et al. 2004). However, it is challenging to develop biological models that can account for the 40- to 50-year "incubation period" between childhood exposure and adulthood disease. To get traction on this problem, a research program needs not only to specify how early-life events get under the skin, but also how they stay there over multiple decades to promote disease later in life.

The biological programming hypotheses advanced by Barker (1997), Hertzman (1999),

and others suggest that during critical periods of development, unfavorable environmental circumstances can program biological systems in ways that persist across the lifespan. These models provide a useful heuristic for thinking about early-life influences, but they did not specify the mechanism by which this occurs. However, recent developments in the biology of epigenetics, transcriptional control circuits, and tissue remodeling have begun to suggest possible biological mechanisms for such developmental influences.

Epigenetics describes stable changes in the activity of a gene that arise without alterations to its DNA sequence (see review by Jirtle & Skinner 2007). Epigenetic alterations allow organisms to establish and maintain different gene expression programs in different cells (which enables cells with the same genetic information to be phenotypically different). Epigenetic control of gene expression occurs in two main ways: either the DNA itself is chemically altered (DNA methylation) or the histone proteins that package DNA into chromosomes are modified. Epigenetic modifications can be mitotically and meiotically heritable, meaning they can be passed across generations of both somatic and germline cells. This allows them to have long-term (and potentially cross-generational) influences (Richards 2006).

Recent evidence suggests that epigenetic modifications constitute one potential pathway through which the early-life environment, both physical and social, influences patterns of genomic activity. For example, studies in animals indicate that some in utero or early-life exposures, such as exposure to cigarette smoking, vitamin B12, and folic acid, can induce epigenetic alterations that persist through the organism's lifetime (Jirtle & Skinner 2007). Moreover, animal models suggest that these alterations may contribute to phenotypic differences and vulnerability to some diseases (see overview by Jirtle & Skinner 2007). Although they can be much more stable over time than are levels of hormone activity or transcription factor activity, epigenetic effects are subject to environmental modification and are therefore less stable than DNA sequence characteristics. A recent study found that human monozygotic twin pairs were epigenetically similar during early life, but showed markedly diverging patterns of DNA methylation and histone acetylation as they aged (Fraga et al. 2005). These disparities were most pronounced in twin pairs who had been separated early in life, suggesting that environmental influences play a major role in driving divergence. Such findings underscore the semiplastic nature of epigenetic modifications.

A provocative research program in animals (Meaney & Szyf 2005) indicates that social exposures in early life can have long-lasting epigenetic and phenotypic influences. This work shows that neonatal rodents who receive high levels of nurturing from their mothers in the first week of life exhibit diminished cortisol responses to stressful experience when they reach adulthood (e.g., Liu et al. 1997). This hormonal resilience to stressors arises from nurturing-induced epigenetic modifications, such as demethylation of DNA and acetylation of histone proteins, that facilitate expression of the GR in hippocampal tissue (Weaver et al. 2004). (Greater expression of GR enables tighter regulation of the hormonal system that controls the release of cortisol.)

Stress-induced epigenetic dynamics provide one mechanistic solution to the incubation problem outlined above. To the extent that future research in humans is able to substantiate Meaney & Syzf's (2005) findings in rodents, epigenetic processes may serve as a mechanistic and conceptual bridge linking temporally distant phenomena. Some preliminary work of this nature has begun to appear. For example, in a cohort of healthy teenagers, we tested associations of SES at different periods of life with current expression of genes that code for GR and other molecules that regulate inflammation (Miller & Chen 2007). Interestingly, the current SES of these subjects did not predict gene expression patterns, but their family's social standing when they were 2–3 years of age did predict patterns. Subjects who spent their early years in a lower-SES setting had lesser quantities of GR mRNA and more mRNA

for proinflammatory genes than did those who spent their early years in a higher-SES setting. This pattern was evident regardless of the subject's current family SES. Though the mechanisms underlying these findings remain unclear, they suggest that low early-life SES may alter the epigenome of immune cells in ways that foster the emergence a proinflammatory phenotype. If corroborated, patterns of this nature could begin to explain early-life influences on diseases of adulthood as well as other temporally distant phenomenon, such as the links between traumatic experiences and health problems that emerge decades later (Dong et al. 2004; Li et al. 2002a,b).

Transcriptional control circuits and posttranslational modification of proteins provide additional molecular mechanisms by which environmental factors can induce persistent alterations in physiologic function. Transcription control circuits involve sequential gene expression relationships that induce positive (or negative) feedback cycles. For example, pathogen-induced inflammatory signaling can activate the proinflammatory cytokine gene *IL1B* (encoding interleukin 1β), which, when it subsequently signals through the IL-1 receptor, can activate the MAP kinase pathway and thereby phosphorylate the GR (Pace et al. 2007). MAP kinase phosphorylation is a posttranslational modification of the GR protein that desensitizes it to the effects of cortisol, resulting in decreased anti-inflammatory signaling from the HPA axis and complementary increases in inflammatory gene transcription by nuclear factor-κB. Continuing inflammatory signaling, in turn, drives increased *IL1B* gene expression, providing a positive feedback cycle that locks out anti-inflammatory signaling and perpetuates inflammation. Many physiologic systems involve such feedback loops and thus provide opportunities for significant environmental influences at one point to shape subsequent physiologic responses to environmental stimuli.

Another biological mechanism that can perpetuate the physiologic effect of transient environmental influences is tissue remodeling. By altering patterns of gene expression in cells, receptor-mediated signaling pathways essentially change the nature of the tissues composed of those cells. This can endow the remodeled tissue with altered sensitivity to subsequent environmental stimuli that persists for the life of a cell or for a generation of its protein structure (e.g., months to years). One example of this comes from the studies of social stress effects on the replication of SIV in rhesus macaques (Sloan et al. 2007b). One consequence of unstable social conditions involves increasing density of SNS neural fibers within the lymph node environment that structures the initiation of immune responses (and serves as a site for viral replication). Stress-induced increase in SNS innervation provides a neurobiological structure that can deliver more norepinephrine into the immunobiological environment of the lymph node in response to a subsequent stressful experience. This dynamic shows similar positive feedback properties to the glucocorticoid resistance dynamic outlined above and can have a substantial impact on immune response to pathogens (Sloan et al. 2007b, 2008). Another instance of tissue remodeling occurs in asthma, when transient inflammatory reactions induce long-term remodeling of airway tissues in ways that render the lungs hypersensitive to subsequent challenges. Thus, the physiologic composition of our current bodies is shaped to some extent by our historical interactions with previous environments. These dynamics provide a concrete molecular manifestation of Barker's (1997) and Hertzman's (1999) notion of biological programming, as well as longitudinal conceptions of allostatic load (McEwen 1998).

The preceding examples describe mechanisms by which relatively transient psychosocial conditions can bring about long-term (even permanent) changes in the ways that cells and tissues behave. However, recent evidence suggests that psychobiologic influences can play out in more temporally dynamic ways as well, where the biology itself becomes a moving target. The most concrete example of this comes from work on chronic stress and cortisol output (see Miller et al. 2007 for a review). It shows

that when chronic stress first begins, there is an initial activation of the HPA axis, which leads to an increased output of cortisol. But as time passes, this activity subsides and cortisol secretion rebounds to normal, and if the stressor persists, to below normal. These findings show that the impact of chronic stress on HPA activity does not unfold in the static and linear fashion that most models in health psychology presume. Instead, the body seems to make use of counterregulatory mechanisms to adapt to the demands imposed by the stressor, just as it does when faced with physical stimuli such as changes in oxygen supply, nutrient availability, or temperature. Characterizing these adaptations and refining models of stress and disease accordingly poses an important challenge for health psychology in the coming decade (for examples of this kind of thinking, see Mohr & Pelletier 2006).

CONCLUSIONS

The health psychology literature has shown substantial growth in phenomenological documentations relating psychosocial factors to disease outcomes (Cohen et al. 2007, Rozanski et al. 1999). The most significant challenge now involves identifying the biological processes mediating those relationships. Success in this arena will strengthen the empirical corpus of health psychology by providing epistemologically satisfying causal explanations for the observed phenomenon and suggesting therapeutic strategies for protecting individuals against the adverse health effects of known risk factors such as low SES, social isolation, stress, and depression. A host of new methodological strategies and conceptual frameworks has emerged to support these endeavors. Some particularly promising technical opportunities involve (*a*) the use of massively parallel molecular assay systems to capture genome-wide patterns of gene transcription, epigenetic dynamics, protein distributions, and posttranslational modifications; (*b*) the advent of sophisticated statistical methods for testing mediational hypotheses in correlational analyses and experimental manipulations of putative mediators; (*c*) the increasing availability of noninvasive imaging systems and validated biomarkers such as CRP that can provide penetrating insights into disease pathophysiology in human populations; and (*d*) meta-analytic statistical strategies that can abstract general theoretical principles from a diverse array of primary literature. Leveraging these methodological advances are new conceptual frameworks for understanding interactions between environmental conditions and health-related physiology, including (*a*) a growing appreciation of inflammation's common contribution to a wide variety of prevalent chronic diseases and its sensitivity to biobehavioral regulation; (*b*) deepening biobehavioral theories that map distinct psychological states and processes onto distinct neuroendocrine and immunologic signatures; and (*c*) new insights into the regulatory plasticity of neuroimmune interactions, including persistent alterations in neurobiological signaling regimes that stem from transient environmental influences (e.g., epigenetic alterations, glucocorticoid resistance, stress-induced innervation dynamics, transcriptional feedback circuits, and tissue remodeling).

Ironically, as the novelty of PNI has waned during the past decade, the field has also begun to yield its first comprehensive mechanistic explanations for biobehavioral relationships in health. That yield emerged first in the context of viral infections, as well-crystallized theories of disease pathogenesis interacted with developing PNI principles to clarify the key role of environmentally sensitive host factors in shaping the biology of viral infections (Glaser et al. 1999, Glaser & Kiecolt-Glaser 2005, Miller & Cohen 2005, Sloan et al. 2007c). As the role of inflammation in atherosclerosis has become more fully appreciated, a rich literature on psychosocial risk factors for CHD has incorporated new pathophysiologic concepts that now promise to define more clearly the specific biological mechanisms involved (Krantz & McCeney 2002, Rozanski et al. 1999). Relationships between stress and the biology of inflammation and tissue regeneration have also

begun to accelerate mechanistic analyses of biobehavioral relationships in cancer (Antoni et al. 2006, Thaker et al. 2006). Progress in all of these areas has been accelerated by the confluence of new perspectives on basic disease pathophysiology and new conceptions of biobehavioral regulation in the common language of molecular biology. In this review, we hope to advance some overarching conceptual approaches that will spur health psychologists to capitalize on these emerging opportunities to the fullest extent possible.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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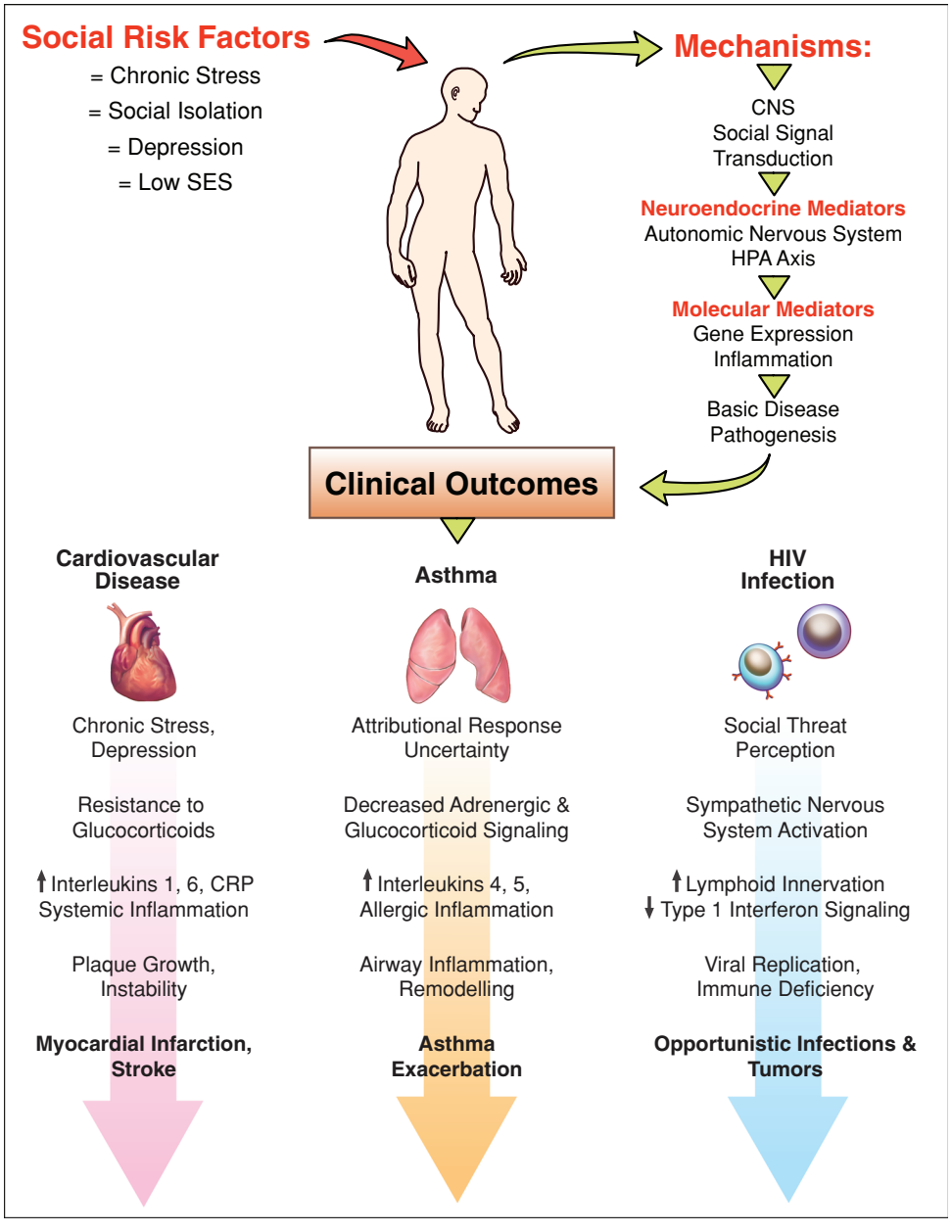

Figure 1

(*Top*) The mechanistic chain of events through which the social world "gets inside the body" to influence disease pathogenesis. (*Bottom*) More-specific mechanistic pathways are hypothesized in the context of heart disease, asthma, and HIV/AIDS.