CHAPTER

23

Social Context as an Individual Difference in Psychoneuroimmunology

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I. INTRODUCTION

Individual differences refer to enduring characteristics that distinguish one organism from another and that are stable over time and across situations. Traditionally, these characteristics have included cognitive, affective, behavioral, and/or genetic traits ascribed to persons or animals. In humans, a large body of work has documented associations between individual differences and morbidity and mortality (Cohen, Doyle, Skoner, Rabin, & Gwaltney, Jr., 1997; Cohen et al., 1995; Cole, Kemeny, & Taylor, 1997; Cole, Kemeny, Taylor, Visscher, & Fahey, 1996; Cole et al., 2001; Kubzansky, Sparrow, Vokonas, & Kawachi, 2001; Miller, Smith, Turner, Guijarro, & Hallet, 1996; Reed, Kemeny, Taylor, & Visscher, 1999; Reed, Kemeny, Taylor, Wang, & Visscher, 1994; Scheier & Bridges, 1995; Scheier et al., 1999), and this work has given rise to mechanistic questions regarding the immunologic correlates of personality characteristics (Cole, Kemeny, Weitzman, Schoen, & Anton, 1999; Davidson, Coe, Dolski, & Donzella, 1999; Denollet et al., 2003; Marsland, Cohen, Rabin, & Manuck, 2001; Miller, Cohen, Rabin, Skoner, & Doyle, 1999; Miller, Dopp, Myers, Felten, & Fahey, 1999; Segerstrom, Taylor, Kemeny, & Fahey, 1998; Strauman, Lemieux, & Coe, 1993; Suarez, 2003; Suarez, Lewis, & Kuhn, 2003). Because several excellent reviews of this area of research have been published recently (Segerstrom, 2000; Segerstrom, 2003; Segerstrom, Kemeny, & Laudenslager, 2001), the goal of this chapter will be to introduce an alternative approach to conceptualizing individual differences, and discuss its implications for conducting and interpreting research in PNI.

Though research on individual differences in PNI has been very fruitful, it has consistently overlooked questions about the origins of cognitive, affective, and behavioral characteristics. In this chapter we will argue that the larger social context is a critical factor in shaping individual differences and needs to be considered more thoroughly in PNI. The term *social context* refers to neighborhood, community, and family influences on an individual. In contrast, much of the individual differences literature isolates the individual and focuses on defining his/her characteristics, without much emphasis on how the larger social context may shape the development of these characteristics. As one representative indicator of this larger social context, we focus here on the role of socioeconomic status (SES). By SES, we refer to an individual's position within a larger social hierarchy, as typically indicated

by social status (e.g., occupation, educational attainment) or material resources (e.g., income, savings).

Focusing on the role of SES in PNI is important for several reasons. First, SES is a construct that simultaneously reflects neighborhood, community, and family influences. At the broadest level, markers of SES can be derived from community characteristics (e.g., the gap between the rich and the poor across a community). At a more proximal level, indicators of SES can be derived from features of a person's neighborhood (e.g., the median home price or rates of violent crime), or the family that he/she is part of (e.g., annual family income or educational attainment). Second, SES is often considered to reflect a stable, enduring characteristic, a necessary quality for an individual difference variable. Although some SES characteristics can change from year to year (e.g., family income), many are fairly consistent across time (e.g., educational attainment). Finally, there is robust evidence that SES at one point in time can have long-lasting impacts on health. For example, early childhood SES has been found to predict health outcomes decades later in adult life, such as cardiovascular disease, stomach cancer, and hemorrhagic stroke (Barker, 1992; Galobardes, Lynch, & Smith, 2004). These observations suggest that SES is an important social context variable that contributes to the development of enduring individual differences across people.

II. SOCIOECONOMIC STATUS AND HEALTH

SES has a profound influence on physical and mental health outcomes. Of all the social and psychological factors studied to date, SES exhibits the strongest and most consistent associations with morbidity and mortality. Individuals lower in SES are more likely to develop illnesses in the first place, to have difficulties managing them, and to die from them, compared with their higher-status peers. This "social gradient" exists for nearly all acute and chronic medical conditions. It also emerges in nearly all countries of the world, regardless of whether their citizens have universal access to care. Lastly, the social gradient persists across the life span, from early childhood to older adulthood (see Adler, Boyce, Chesney, Folkman, & Syme, 1993; Chen, Matthews, & Boyce, 2002; Marmot, Kogevinas, & Elston, 1987; Townsend & Davidson, 1982; Williams & Collins, 1995, for reviews).

SES also is associated with a wide variety of psychological variables. These include traditional individual difference variables, such as hostility, optimism, depression, and anxiety (Adler et al., 1994; Barefoot et al., 1991; Gallo & Matthews, 2003; Kubzansky, Sparrow, Vokonas, & Kawachi, 2001). Furthermore, low SES is associated with poor health behaviors, such as increased risk of smoking and decreased physical activity (Adler et al., 1994; Cohen, Kaplan, & Salonen, 1999; Lynch, Kaplan, & Salonen, 1997). Finally, evidence suggests that individuals from different SES backgrounds have different types of life experiences. For example, lower SES individuals are more likely to be exposed to stressful life events and are more likely to perceive stress in their lives (Brady & Matthews, 2002; Chen, Langer, Raphaelson, & Matthews, 2004; Cohen et al., 1999).

Taken together, these findings suggest that SES is an individual difference variable that has profound effects on health and well-being. This highlights the importance of studying SES from a PNI perspective in order to understand mechanisms for how SES "gets under the skin" to influence health outcomes. Furthermore, SES clearly has psychosocial influences, underscoring the importance of considering SES as a psychologically relevant individual difference variable in PNI studies. In the next section, we briefly discuss possible pathways between SES and immune functions.

III. PATHWAYS LINKING SOCIOECONOMIC STATUS AND IMMUNE FUNCTIONS

Why would a person's SES influence the functions of his/her immune system? Although there are many potential answers to this question, they can usually be placed into one of two categories of explanation, depending on whether they emphasize SES's role in fostering *exposure* versus *vulnerability*.

Exposure hypotheses maintain that a person's SES influences his/her chances of coming into contact with stimuli (exposures) that modify the immune response. These stimuli can range from micro-organisms that give rise to infectious disease, to environmental pollutants that set off inflammatory processes in the lung, to psychosocial stressors such as negative life events and community violence. Although these stimuli differ from one another in many respects, and influence immune functions through disparate mechanisms, what they share in common is a robust social gradient. For example, sanitation, environmental pollution, and violence vary by SES (Evans, 2004; Selner-O'Hagan, Kindlon, Buka, Raudenbush, & Earls, 1998). In addition, robust SES differences exist in the frequency of stressor exposure (Attar, Guerra, & Tolan, 1994; Brady et al., 2002; Garbarino, Kostelny, & Dubrow, 1991) and

in the way that stressors are appraised (Chen et al., 2004; Cohen et al., 1999). This cumulative stressor burden is expected to give rise to immune system dysregulation among low SES individuals, rendering them vulnerable to diseases that are immunologically resisted or mediated (Herbert & Cohen, 1993; Segerstrom & Miller, 2004). See Figure 1 for a graphical depiction of the exposure model.

There are several mechanisms through which stressful experiences could "get inside the body" to modify immunity. They include activation of autonomic fibers descending from the brain to lymphoid organs, stress-related secretion of hormones and neuropeptides that regulate leukocyte function, or changes in coping behaviors such as smoking or sleeping (Ader, Cohen, & Felten, 1995; Cohen & Williamson, 1991).

Behaviors such as cigarette smoking, alcohol consumption, and a sedentary lifestyle also can be viewed as potential mechanisms of exposure. These behaviors are more frequently observed among low SES individuals (Adler et al., 1994; Cohen et al., 1999; Lynch et al., 1997), and they are known to modify various immune functions (Cohen, Miller, & Rabin, 2001; Kiecolt-Glaser & Glaser, 1988). However, social disparities in morbidity and mortality persist after statistical adjustment for health practices, suggesting that behavior is not likely to be the primary mechanism of action for SES (Lantz et al., 1998; Lantz et al., 2001).

In contrast to exposure hypotheses, vulnerability hypotheses maintain that low SES makes individuals more vulnerable when an exposure occurs. That is, among low SES individuals, higher levels of exposure will relate to greater dysregulation of immune function. In contrast, high SES will buffer individuals from the effects of exposure, such that greater exposure will be only weakly or not associated with immune dysregulation. Thus, this hypothesis argues that low SES individuals have a more pronounced response to an equivalent exposure (stimulus) compared to high SES individuals. See Figure 2. Much of this work has been conducted with testing stress as a type of exposure. In this context, the vulnerability hypothesis predicts that low SES individuals would exhibit heightened immunologic dysregulation during times of high stress compared to low stress; in contrast, high SES individuals will be buffered and show few immune differences during high stress versus low stress times.

Why would low and high SES individuals differ in their response to an identical stressor? One hypothesis is that people continuously appraise ongoing stressful circumstances along dimensions of threat and manageability (Lazarus & Folkman, 1984). To the extent that circumstances are evaluated as posing significant threat and exceeding coping resources, they elicit a cascade of emotional, behavioral, and hormonal responses, which ultimately result in dysregulation of various immune system functions (Cohen & Williamson, 1991; Segerstrom & Miller, 2004). Moreover, a person's tendency to appraise stressors as threatening is shaped by his/her SES (Chen & Matthews, 2001; Chen & Matthews, 2003). By virtue of living and working in settings that are unpredictable and sometime dangerous, lower SES persons develop a tendency to interpret situations as potentially threatening, even when the extent of danger is ambiguous. This vigilant cognitive style results in interpretations of an equivalent stressor as more threatening among lower SES individuals. This response strategy in turn may activate stress-response systems unnecessarily, and over time this may contribute to cumulative wear-and-tear on the endocrine and immune systems (Chen et al., 2004; McEwen, 1998).

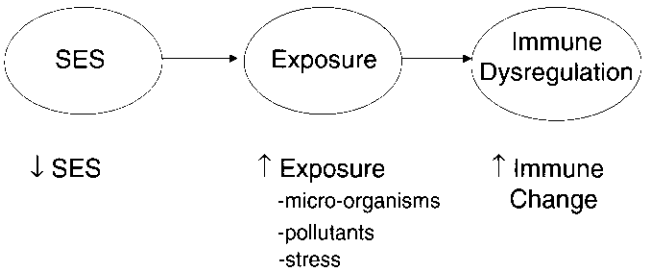

FIGURE 1 Exposure model. Low SES individuals receive higher levels of exposure to micro-organisms, pollutants, and stressors, and in turn, higher levels of exposure are associated with greater immune dysregulation.

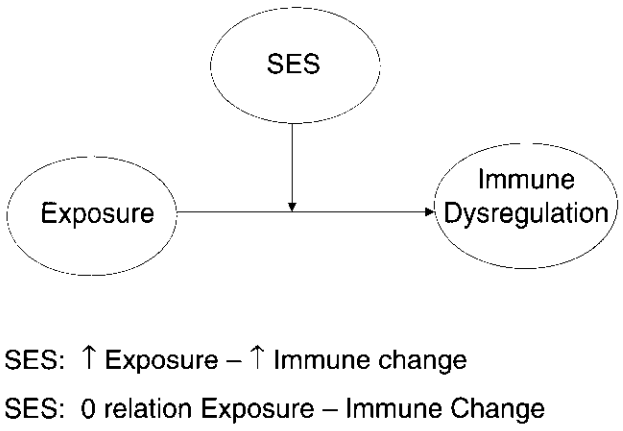

FIGURE 2 Vulnerability model. The relationship between exposure and immune function depends on SES. Among low SES individuals, high levels of exposure are related to greater immune dysregulation. In contrast, high SES buffers individuals from the effects of exposures, such that there is no relationship between exposure and immune dysregulation in this group.

A second aspect of the vulnerability hypothesis suggests that a person's SES governs the types of coping resources he/she has available and can utilize during stressful encounters. Persons of lower SES by definition have fewer economic and educational resources than their high-SES peers; these disparities are likely to accentuate the impact of life stressors like job loss or chronic illness in the family. In support of this hypothesis, previous research has documented that providing individuals with resources reduces cardiovascular reactivity during an acute laboratory stressor among low SES, but not high SES, individuals (Chen, 2005). Thus, these theories suggest that the reasons why low SES individuals may show heightened biological responses compared to high SES individuals to equivalent exposures have to do with psychological processes such as threat appraisals and coping.

IV. DEFINING AND MEASURING SOCIOECONOMIC STATUS

SES is a multi-dimensional construct, and the measures one chooses of SES can reflect different underlying conceptualizations about what SES means (Winkleby, Jatulis, Frank, & Fortmann, 1992). One traditional approach to conceptualizing SES is as an indicator of a person's status or standing within society. Researchers have termed these "prestige-based measures of SES," as they indicate how a person is regarded within the community. Commonly used prestige-based indicators include education and occupation (Krieger, Williams, & Moss, 1997; Winkleby et al., 1992), with more advanced training and more prestigious jobs viewed as higher status.

Others have argued for a resource-based model of SES, which suggests that the critical component of SES is the material resources a person possesses. These assets, including family income, assets, and wealth, are hypothesized to play a role in determining both health status and health trajectories over time in a family (Krieger et al., 1997; Lynch, Smith, Kaplan, & House, 2000).

In contrast to these two more objective approaches, other researchers have argued for a more subjective, or relative, approach to measuring SES. This approach is based on the notion that most individuals do not understand SES in terms of absolute dollars, but rather in terms of where they stand relative to their peers, and that an individual's *perception* of his/her SES or social standing will be more important to health outcomes than objective measures (Adler, Epel, Castellazzo, & Ickovics, 2000).

In addition, SES can be measured at multiple levels (Krieger et al., 1997). For example, one could measure characteristics of the community, neighborhood, family, or individual. Community measures include factors such as the level of income inequality in a society, or the level of social capital (community norms for cooperation and behavior) (Kawachi, Kennedy, Lochner, & Prothrow-Stith, 1997; Wilkinson, 1992). Neighborhood SES measures are narrower than community measures, and represent an aggregate measure of the group of individuals living in a neighborhood. These include indicators such as the percentage of adults with less than high school education in the neighborhood, median family income of the neighborhood, and percentage of people who own their own homes in the neighborhood. These characteristics describe the larger context that an individual lives in.

At the family and individual levels, SES measures include direct assessments of the individual participant or the household that the participant lives in. Family measures include those described above, such as the income and savings of all family members living in a household. In contrast, individual SES measures focus on just the study participant, and could include either objective indicators, such as the individual's occupation or educational attainment, or the subjective indicators described above, such as perceived social status.

These various approaches highlight the importance of understanding the measurement approach when interpreting findings on SES and PNI. In addition, it also indicates the importance for future researchers in this area to consider the ways in which SES might exert effects on their immune outcomes of interest, and to choose theoretically meaningful approaches to measuring SES when designing PNI studies. For example, stronger associations with resource-based SES measures such as income and savings might suggest that more money allows families to afford higher quality medical care, which would presumably have effects on disease processes. In contrast, stronger associations with prestige-based SES measures such as educational attainment might suggest that higher SES families have better knowledge about healthy lifestyles, which in turn may lead to better health behaviors with immunological consequences. Finally, stronger associations with subjective SES measures might suggest that perceptions of social standing are related to the control one perceives over one's life, or the degree to which one utilizes proactive coping strategies for dealing with stress, both of which may have implications for activation of stress-response systems.

V. EVIDENCE OF SOCIOECONOMIC STATUS ASSOCIATIONS WITH IMMUNE FUNCTIONS

This section describes existing research on SES and immunity in humans. Following the conceptual distinction introduced earlier, studies are grouped according to whether they emphasize *exposure* versus *vulnerability*, and also according to kinds of immune system outcomes they include. Because this is a new area of inquiry, most research focuses on the simple question of whether SES and immune outcomes are related, without attempting to identify mechanisms that might be responsible for such an association. As we note, this will be an important direction for later research.

A. Exposure Hypothesis

Studies guided by the exposure hypothesis examine associations between SES indicators and immune functions. The better research in this area goes a step further and seeks to identify potential underlying mechanisms, such as SES-related disparities in pathogen exposure, environmental pollutants, health practices, or stressful experience.

B. Studies in Community Populations

A number of these studies have shown associations of SES with inflammatory molecules involved in the pathogenesis of coronary heart disease (CHD). For example, healthy adults from lower SES groups (as defined by a combination of education and income) had higher levels of CRP, IL-6, TNR-α, fibrinogen, and homocysteine (Panagiotakos et al., 2005). Adults from lower occupation groups had higher levels of CRP, IL-6, and serum amyloid A (though no differences were found for adhesion molecules that reflect endothelial activation) (Hemingway et al., 2003), and higher levels of fibrinogen (Brunner et al., 1993). Being unemployed also was associated with higher levels of CRP, although no differences in CRP were found for other SES markers such as education, car and home ownership (Danesh et al., 1999). Finally, adults from a low income group had higher levels of heat shock protein 60 compared to those from a high income group (Lewthwaite, Owen, Coates, Henderson, & Steptoe, 2002). Heat shock protein 60 is a protein released by cells that have faced trauma, such as heat, injury, or infection, and high levels have been related to CHD (Zhu et al., 2001).

Other studies have examined immune markers different from those implicated in CHD. For example, one study measured the presence of the immunoglobulin secretory IgA (or sIgA) in maternal breast milk. Lower household income was associated with higher sIgA (Groer, Davis, & Steele, 2004). These findings suggest that low SES mothers may have been exposed to infectious micro-organisms to a greater extent than high SES mothers. At the same time, however, higher concentrations of sIgA may be beneficial for breastfeeding infants, who receive most of their mucosal immune protection through maternal transfer of antibody in milk.

C. Studies with Relative SES Measures

Another study utilized a novel approach of measuring SES to investigate associations with immune variables. All of the above studies have relied on objective indicators of SES, such as education or occupation. However, families vary greatly in the extent to which they spend money on material possessions, regardless of their objective status. Dressler (Dressler, 1990; Dressler, Bindon, & Neggers, 1998) has argued that the discrepancy between outward displays of prestige (via material possessions) and actual objective circumstances (via education or occupation) is an indicator of "lifestyle incongruity," and that higher levels of lifestyle incongruity are detrimental because they create stresses on the family. Consistent with this line of reasoning, one study found that in adolescents greater lifestyle incongruity (greater material possessions relative to objective circumstances) was associated with more antibody to the latent Epstein-Barr virus (EBV) (McDade, 2001). Higher levels of antibodies suggest that latent EBV may have been reactivated, either by stress hormones, poor immune control, or other mechanisms (Glaser & Gottlieb-Stematsky, 1982). Given that EBV plays a role in the pathogenesis of infectious mononucleosis, these findings could have implications for explaining some of the SES gradient in infectious disease.

D. Studies in Chronically Ill Populations

Finally, one study examined associations of SES with immune markers in the context of a chronic inflammatory disease. Adolescents diagnosed with persistent asthma were recruited from either low SES or high SES neighborhoods (based on the percentage of people living below poverty in each neighborhood). Blood was drawn, and cells were stimulated with a combination of phorbol myristate acetate and ionomycin to induce the production of cytokines. Researchers have hypothesized that certain cytokines are impor-

tant for the orchestration of cellular events related to airway inflammation and hyper-responsiveness (Chung & Barnes, 1999). For example, Th-2 cell secretion of IL-4 induces B-cells to produce IgE antibodies, which initiate an inflammatory cascade leading to airway constriction and mucus production (Bacharier & Geha, 2000). Th-2 cell secretion of the cytokine IL-5 has been found to increase eosinophil production, which also promotes airway inflammation and obstruction (Kamfar, Koshak, & Milaat, 1999; Ying et al., 1997). More recently, some researchers have argued that the cytokines that Th-1 cells produce (e.g., IFN-γ) also are elevated in patients with asthma, and can induce airway inflammation (Busse & Lemanske, 2001; Hansen, Berry, DeKruyff, & Umetsu, 1999; Holtzman, Sampath, Castro, Look, & Jayaraman, 1996; Marguet, Dean, & Warner, 2000). Thus, this study investigated stimulated production of IL-4, IL-5, and IFN-γ. Adolescents with asthma from low SES neighborhoods displayed significantly greater production of IL-5, IFN-γ, and marginally greater production of IL-4 compared to adolescents with asthma from high SES neighborhoods (Chen, Fisher, Jr., Bacharier, & Strunk, 2003). See Figure 3. These findings suggest that within the context of a chronic disease, low SES adolescents may exhibit heightened inflammatory responses to pathogens, and that the specific nature of these responses is consistent with pathways to more severe exacerbations of asthma.

E. Vulnerability Hypothesis

Studies examining the vulnerability hypothesis often utilize the acute-stress paradigm. This entails bringing participants into the laboratory and collecting blood from them during a resting baseline. Participants then engage in a brief stressor, such as impromptu public speaking or pressured mental arithmetic, and additional blood is collected after the stressor. The vulnerability hypothesis is supported when low SES participants exhibit greater stressor-induced immune dysregulation compared with high SES participants.

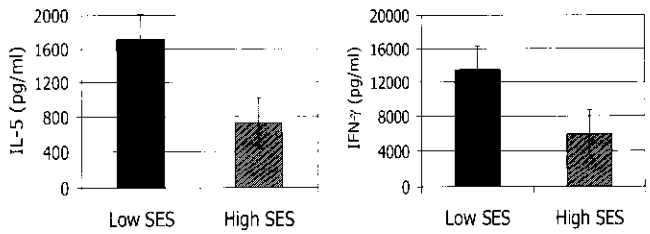

FIGURE 3 Evidence for exposure model: Low SES adolescents with asthma have higher levels of stimulated production of IL-5 and IFN-γ compared to high SES adolescents with asthma.

Importantly, under this hypothesis SES differences are predicted to emerge during stressful circumstances, rather than during the baseline period.

F. Laboratory Stress Paradigms

A number of studies have examined the vulnerability hypothesis in relation to inflammatory molecules implicated in CHD. These studies have been conducted by one research group and have all used a similar paradigm. Healthy adults underwent two acute stress tasks. One involved tracing an image that could only be seen in a mirror, as quickly and accurately as possible. The second involved identifying as quickly as possible the colors of color words that were printed in incongruent colors (e.g., the word *red* printed in blue. This is also known as the Stroop task). These tasks typically lasted 5 minutes each. Blood was drawn at baseline, in some studies immediately after the acute stressors, and then during a recovery period (ranging from 30–120 minutes post-stressor across the various studies). SES was defined by participants' occupational status, for example, higher status jobs being managerial positions, and lower status jobs being clerical positions.

One of these studies found partial support for the vulnerability hypothesis. Lower SES participants had higher circulating concentrations of the inflammatory cytokine interleukin-6 (IL-6) 120 minutes after the stressor ended compared with higher SES participants (Brydon, Edwards, Mohamed-Ali, & Steptoe, 2004). No SES differences in IL-6 were evident at baseline, or at 30 or 75 minutes after the stressor. Given that protein synthesis requires a minimum of 1–2 hours to occur, 30–75 minutes may have been too soon to detect stress-related boosts in IL-6 expression. Regardless, if the findings at 120 minutes prove to be robust, they could help to explain the SES gradient in cardiovascular disease, as inflammatory processes have a key role in the development, progression, and clinical expression of atherosclerosis (Libby, Ridker, & Maseri, 2002; Ross, 1999).

In contrast, several of this group's other studies have found SES differences in inflammatory molecules during resting periods, but this difference did not change during or after participants were exposed to a stressor. For example, adults who are low in SES by virtue of having a low-prestige occupation (or lower education or income) showed elevated concentrations of the inflammatory molecule C-reactive protein during a resting baseline (Owen, Poulton, Hay, Mohamed-Ali, & Steptoe, 2003). CRP is a marker of systemic inflammation, and high levels are associated with CHD risk (Ridker, 2003; Ridker, Hennekens,

Buring, & Rifai, 2000). They also showed higher numbers of total lymphocytes, T lymphocytes, and natural killer cells at baseline compared with higher SES adults, but SES disparities did not increase in magnitude 1 or 45 minutes after the stressor ended, as the vulnerability hypothesis would predict (Owen et al., 2003).

In another study by this group, women with lower occupational status had higher IL-6 at baseline, but again SES differences did not change in magnitude after the stressor. There also were no SES disparities for men (Steptoe, Owen, Kunz-Ebrecht, & Mohamed-Ali, 2002). Other studies from this group have focused on coagulation processes involved in CHD progression. This work has yielded a similar pattern of findings. Participants with lower SES showed higher levels of coagulation markers such as fibrinogen (Steptoe et al., 2003a), leukocyte-platelet aggregate, and monocyte-platelet aggregate (Steptoe et al., 2003b) during resting-baseline periods. However, the SES disparities did not change in magnitude from the resting baseline to after the stressor. Finally, one study found quadratic effects of SES on inflammatory molecules linked to CHD. Adults in the intermediate SES group had the highest levels of the inflammatory cytokines tumor necrosis factor-α (TNF-α and interleukin-1 receptor antagonist (IL-1ra) compared to those in the low or high SES groups at baseline. Again, these disparities did not diverge further during or after the stressor (Steptoe et al., 2002). Collectively, these findings suggest that SES differences primarily exist under basal conditions, supporting the exposure hypotheses (SES differences in immune markers evident across different conditions). These studies on the whole did not find evidence suggesting that among low SES individuals, there is a stronger relationship between exposure to stress and immune function compared to among high SES individuals (as the vulnerability hypothesis would suggest).

G. Life Experiences with Stress

It is important to remember that these studies focused on acute stressors in the laboratory, and the artificial nature of these tasks raises questions about their generalizability to the real world. A project conducted by a different research group found support for the vulnerability hypothesis when low and high SES persons were compared in the midst of a real-life chronic stressor. In this study, healthy adults were recruited who were either undergoing a major life chronic stressor (having a child being treated for pediatric cancer) or were under no chronic stress (having medically healthy children and no other major life stressors). Parents underwent blood draw, and their cells were co-incubated *in vitro* with lipopolysaccharide (a bacterial product that stimulates cytokine production) and dexamethasone (a synthetic form of the hormone cortisol, which is a potent inhibitor of inflammation), and subsequent production of IL-6 was measured. This assay tests leukocyte sensitivity to the inhibitory properties of glucocorticoid hormones, which *in vivo* play a key role in regulating the magnitude and duration of inflammation. Interestingly, chronic stress-related alterations in the immune system were evident only among low SES participants. That is, parents of cancer patients showed reduced sensitivity to the anti-inflammatory properties of dexamethasone compared to parents of healthy children, but this was true only if they had lower levels of education (defined as a high school diploma or less). In parents of cancer patients who had some college education, there were no detectable alterations in glucocorticoid sensitivity relative to controls (Miller, 2002). See Figure 4. These findings suggest that low SES individuals facing chronic stressors may have disrupted mechanisms for regulating inflammation, which if sustained could place them at risk for conditions involving excessive inflammation, such as cardiac, allergic, and autoimmune diseases (Miller, Cohen, & Ritchey, 2002). More generally, these findings provide support for a vulnerability hypothesis of SES, at least in the context of real-world stressors that are severe and chronic.

H. Vulnerability to Viral Challenge

A handful of studies have examined a modified version of the vulnerability hypothesis. In this view

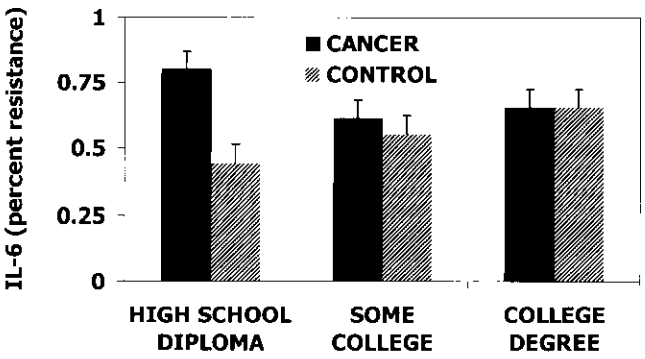

FIGURE 4 Evidence for vulnerability model: Among low SES individuals, high exposure to chronic stress (being a parent of a child with cancer) is associated with reduced sensitivity to the anti-inflammatory properties of dexamethasone compared to low exposure to chronic stress (being a parent of a healthy child). In contrast, among higher SES individuals, exposure to chronic stress is not related to sensitivity to dexamethasone.

SES determines the efficacy of a person's immune response to infectious challenge rather than (or perhaps in addition to) his/her response to stressful experience. The idea here is that SES influences the immune system's capacity to eradicate invading pathogens, or modifies the nature and severity of clinical symptoms a person experiences once infected. This paradigm usually involves assessing healthy participants on a variety of SES variables and then exposing participants to a rhinovirus that causes upper respiratory infection. Participants are quarantined and monitored for signs of objective infection (viral shedding and antibody production) and clinical illness (mucus production and nasal congestion). Participants are considered to have a "cold" if they meet criteria for both infection and illness.

One group of researchers has documented several SES-related findings using this paradigm. For example, adults who were unemployed (or underemployed) were three to four times more likely to develop a cold after rhinovirus exposure compared with adults who had sufficient work (Cohen et al., 1998). In another study, this group showed that SES during early periods of life has important consequences for disease susceptibility. Adults who had lower SES when they were children—as indicated by their parents not owning a home—were more likely to develop a cold following viral exposure (Cohen, Doyle, Turner, Alper, & Skoner, 2004). This was a dose-response association, such that the more years a family did not own a home, the more likely the participant was to develop a cold. Interestingly, owning a home later in life—either during adolescence or adulthood—did not attenuate these associations. This suggests that early childhood may be a critical period during which SES shapes the immune system in a fashion that cannot be "undone" by later improvements in a person's social status.

Finally, in addition to objective indicators of SES, these researchers also investigated the role of subjective indicators of status. Before exposure to the virus, participants were asked to rate where they stood in their own community relative to others. Adults who perceived themselves to be lower in social status were more likely to develop infection following exposure to a rhinovirus (Cohen, 1999).

I. Response to Vaccination

Lastly, one study from another research group utilized a slightly different paradigm for examining SES differences in vulnerability to immune challenge. Rather than exposing participants to viruses that cause the common cold, these investigators tested the associations of SES with responses to vaccination for rubella in adolescent girls. After vaccination, adolescents were classified as either infected with the rubella virus (being seronegative at the start of the study, then showing at least a four-fold increase in rubella antibody titers), or as showing no change in antibody titers (due to being seropositive at the start of the study). These researchers found that antibody response was associated with different behavioral effects, depending on the SES of the adolescents. Among low SES girls, those who showed an antibody response to vaccination reported more depression, attention problems, and delinquent behaviors 2–10 weeks after vaccination compared to those who did not respond to vaccination (Morag, Yirmiya, Lerer, & Morag, 1998). In contrast, among middle and high SES girls, there were no behavioral differences between those who did and did not show antibody response to vaccination. Research indicates that inflammation following pathogen exposure can produce a constellation of adjustments known as sickness behavior (Maier & Watkins, 1998; Yirmiya, 1996). These behaviors are thought to be similar to depression and can include negative mood, difficulty concentrating, and anhedonia. Thus, the findings from the above study suggest that low SES individuals may be particularly vulnerable to sickness behaviors that result from infectious challenges.

J. Potential Pathways between SES and the Immune System

In addition to investigating associations of SES with immune markers, several of the above studies have also tested whether different mechanisms may account for relationships between SES and immune markers. These mechanisms include ones described earlier, such as stress and health behaviors, as well as other pathways such as social support and the endocrine system. Typically, these studies statistically control for possible mechanistic pathways, and compare the relationship of SES and immune markers prior to and after controlling for these variables.

In their study on production of cytokines implicated in asthma, Chen et al. (2003) found that adolescents with asthma from low SES neighborhoods had heightened production of IL-5 and IFN-γ compared to adolescents with asthma from high SES neighborhoods. Stress was measured in this study both in terms of life stress exposure and perceptions of stress. When stress was included as a control variable, the relationship between SES and cytokine production decreased by 38–76%, and was no longer significant (Chen et al., 2003), suggesting that stress is a critical pathway linking SES and cytokine production in adolescents with asthma.

With respect to health behaviors, a number of studies have tested the effects of controlling for health behaviors. Some studies have found that controlling for health behaviors somewhat reduces the association between SES and immune markers. For example, controlling for smoking, alcohol, exercise, and diet reduced the relationship between low SES and high fibrinogen levels to non-significant in women (but not men) (Brunner et al., 1993). On the other hand, controlling only for smoking did not reduce the association between SES and fibrinogen to non-significant in another study (Steptoe et al., 2003a). This may be because the constellation of health behaviors as a whole best accounts for the SES-fibrinogen relationship, or because factors such as alcohol use or exercise are more important to the SES-fibrinogen relationship than smoking.

In contrast, the association between SES and other inflammatory markers, including CRP, IL-6, TNF-α, fibrinogen, and homocysteine remained significant after controlling for smoking, diet, physical activity, and medication compliance (Panagiotakos et al., 2005). Similarly, in the viral cold studies described above, controlling for smoking, alcohol, exercise, sleep, and vitamin C consumption slightly reduced the magnitude of the relationship between unemployment and risk of cold; however, the risk of cold for those facing unemployment was still significant (Cohen et al., 1998). In addition, controlling for smoking, alcohol, exercise, and sleep did not diminish the relationship between perceived social status and likelihood of developing a cold (Cohen, 1999). Taken together, these findings suggest that as they have been assessed to date, there is not much evidence that health behaviors play a major role in relationships between SES and inflammatory processes. However future studies that conduct more thorough and objective assessments of factors such as sleep, exercise, and diet may reveal greater support for the role of health behaviors in SES-immune relationships.

Other pathways that have been tested include social support and endocrine measures. No evidence has been found for either of these processes as pathways. For example, the relationship between lower income and higher heat shock protein 60 remained significant after controlling for social isolation (Lewthwaite et al., 2002). The relationship between unemployment and colds remained significant after controlling for the diversity of a person's social network (Cohen et al., 1998). With respect to endocrine measures, the association between unemployment and colds, as well as between perceived social status and colds, remained significant after controlling for epinephrine and norepinephrine (Cohen et al., 1998; Cohen, 1999).

Taken together, these findings suggest that additional research is needed to uncover the mechanisms by which SES exerts effects on the inflammatory processes. Perhaps the most promising mediator is stress; however, only one study has tested the role of stress on SES and immune markers (Chen et al., 2003). Thus far, health behaviors, social support, and endocrine measures do not have much evidence supporting their mediational role. Future studies should explore the role of stress in greater depth, as well as test other possible mediators psychosocially (e.g., trait variables such as locus of control) and biologically (e.g., cortisol).

VI. CONCLUSIONS

Though it has received scant attention in the PNI literature thus far, SES is emerging as an important individual difference characteristic. Persons of low SES exhibit various indicators of immune dysregulation when they are at rest, including heightened expression of inflammatory and coagulation molecules involved in CHD, and greater production of cytokines that are responsible for the symptoms of asthma. Although low SES does not seem to render people especially vulnerable to immune dysregulation following acute lab stress, there is preliminary evidence that it amplifies the biological consequences of severe and chronic stressors in real-life settings. Perhaps most compelling are the influences of SES following infectious challenge; persons of lower status exhibit heightened susceptibility to respiratory infection and sickness behavior. The mechanisms underlying these findings have not yet been elucidated. However, with further efforts in this exciting new area of PNI research, we will soon have a better understanding of how social context "gets under the skin" to influence well-being and health outcomes in such a profound fashion.

Acknowledgments

Support for this chapter was provided by National Institutes of Health grant HL073975, the Canadian Institutes of Health Research, and the Michael Smith Foundation for Health Research.

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