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Multilevel Integrative Analyses of Human Behavior: Social Neuroscience and the Complementing Nature of Social and Biological Approaches

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Social and biological explanations traditionally have been cast as incompatible, but advances in recent years have revealed a new view synthesized from these 2 very different levels of analysis. The authors review evidence underscoring the complementing nature of social and biological levels of analysis and how the 2 together can foster understanding of the mechanisms underlying complex behavior and the mind. Specifically, they review the utility of considering social influences on biological processes that are often viewed as outside the social domain including genetic constitution, gene expression, disease, and autonomic, neuroendocrine, and immune activity. This research underscores the unity of psychology and the importance of retaining multilevel integrative research that spans molar and molecular levels of analysis. Especially needed in the coming years is more research on the mechanisms linking social and biological events and processes.

Social and biological approaches to human behavior have traditionally been contrasted as if the two were antagonistic or mutually exclusive. Consider the conclusion in the following news report, an interpretational bias that can also be found in the scientific literature:

> Just five days after President Clinton announced in his State of the Union address, that the Justice Department is preparing to sue tobacco companies to recover money that Medicaid spends treating smoking-related diseases, scientists have given the companies a possible out. In papers published this week, geneticists report that a specific gene can affect whether or not someone starts smoking—and, if he does, whether he becomes addicted. People who have one particular gene, which is involved in the brain's use of the molecule dopamine, are less likely to smoke than those without the gene; if they do smoke, they start later and have an easier time quitting. So maybe it's not those Joe Camel ads after all. (Howard, O'Donnell, Stevenson, & Oxfeld, 1999, p. 6)

The thesis of this article is that the mechanisms underlying mind and behavior are not fully explicable by a biological or a social approach alone but rather that a multilevel integrative analysis may be required. All human behavior, at some level, is biological, but this is not to say that biological reductionism yields a simple, singular, or satisfactory explanation for complex behaviors or that molecular forms of representation provide the only or best level of analysis for understanding human behavior (Cacioppo & Berntson, 1992b; Gottlieb, 1998). Molar constructs such as those developed by the social sciences provide a means of understanding highly complex activity without needing to specify each individual action of the simplest components, thereby offering an efficient means of describing the behavior of a complex system (Cacioppo & Berntson, 1992a; Turkheimer, 1998).

Within the discipline of psychology, the tensions between biological and social approaches surface in biopsychology/behavioral neuroscience and social psychology. Biopsychology focuses on neural substrates and production mechanisms for behavior, whereas social psychology emphasizes multivariate systems and situational influences in studies of the impact of human association on mind and behavior. Human biology is anchored in concrete anatomy and genetics, providing fundamental elements from which to draw interconnections and with which to construct theory. The social world, in contrast, is a complex set of abstractions representing the actions and influences of and the relationships among individuals, groups, societies, and cultures. The differences in levels of analysis have resulted in distinct histories, research traditions, and technical demands, leaving what some regard both as an impassable abyss between social and biological approaches and as evidence of the impending demise of psychology as a discipline.

> Psychology lacks a clear identity. . . . Some of the vectors along which the subdisciplines have matured . . . have developed at obtuse angles to one another, and as the distance between them grows, they strain against the departmental membrane and are irritated by the require-

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> ments of common membership in a distended administrative unit. Social and biopsychology are an example. Most biopsychology students consider a core course in social psychology to be an impediment. . . . I assume that our students in social psychology reflect that sentiment about their core experience in biopsychology. . . . The centrifugal forces in psychology departments today far exceed the centripetal force of the departmental membrane. (Scott, 1991, p. 975)

The abyss between biological and social levels of organization is a human construction, however, one that must be bridged to achieve a complete understanding of human behavior.

Not long ago, it was thought that a set of master genes activated the DNA necessary to produce the appropriate proteins for development and behavior (Crick, 1970). The architects of this construction were conceived as the forces of evolution operating over millennia; the builders were conceived as encapsulated within each living cell far from the reach of personal ties or sociocultural influences. Human biology, however, has evolved within a fiercely social world, provides potentials and constraints for representation and behavior attuned to this social world, and is shaped profoundly by the social world.

The full complement of DNA is in each cell of the newborn, but evidence is mounting that signals from the internal and external environment play an important role in the constitution and transcription of DNA and in the translation of RNA to proteins (see, e.g., Bronfenbrenner & Ceci, 1994; Gottlieb, 1998). A distinction between genotype and phenotype that is situationally determined is evident in infants born with pheneylketonuria (PKU). These infants lack the appropriate gene for an enzyme critical for protein metabolism (McClintock, 1979). This results in the inability to digest a particular amino acid present in certain foods (e.g., milk, dairy products), which in turn leads to the accrual of this amino acid and its metabolites, which can be toxic. When the levels of these compounds are high, normal neurological development is disrupted, and severe, irreversible mental retardation results. In most cases, however, it is possible to greatly attenuate this mental retardation by changing the diet of these infants until the critical period of neurological development has passed. Thus, PKU is an inherited behavioral trait that is innate in a genetic sense but not innate in the developmental sense because its occurrence can be diminished by modifying what the infant is fed (McClintock, 1979).

Early life experiences have also been shown to affect phenotypic expression in animals. Rats raised in enriched environments show more dendritic branching (Greenough, Juraska, & Volkmar, 1979), more postsynaptic dendritic spines (Globus, Rosenzweig, Bennett, & Diamond, 1973), and larger and more numerous synapses per neuron (Turner & Greenough, 1985). When a restricted sector of somatosensory cortex is deprived of its normal pattern of activation, the affected cortex becomes largely reactivated by inputs from adjoining and nearby skin fields (Kaas, Merzenich, & Killackey, 1983). Maternal stimulation during rearing affects the number of fibers in the corpus callosum and related areas in the central nervous system (see, e.g., Juraska & Kopik, 1988). Although the generalization of these findings from animals to humans needs to be demonstrated, they suggest clear connections rather than an impassable abyss between biological and social levels of organization. Studies that span biological and sociocultural levels of analysis are needed to examine these connections in humans and to plumb causal (including possible reciprocal) relationships and underlying mechanisms.

The nervous, endocrine, and immune systems were also once thought to function independently, outside the reach of the personal ties and cultural influences. Both of these simplifying assumptions are understandable given the complexities involved, and studies guided by these assumptions have led to impressive advances in knowledge. An inherent limitation in such studies, however, is that they are blind to linkages across these systems and to the mechanisms underlying these interactions. Research on the molecular aspects of neuroimmunomodulation, for instance, has revealed these to be integrative systems that communicate by a common biochemical language (i.e., shared ligands—compounds, such as cytokines, hormones, and neurotransmitters, that bind to receptors and exert functional actions). The discovery of adrenergic (see Madden, Thyagarajan, & Felton, 1998) and glucocorticoid (see, e.g., Bauer, 1983; Glaser, Kutz, MacCallum, & Malarkey, 1995) receptors on immune cells provided avenues through which the nervous and endocrine systems could exert their influence on immune function (see McCann et al., 1998). The immune system also acts on the central nervous system, as illustrated by studies of a peripheral immune cytokine (lymphocyte secretion) that is transduced into a neuronal signal and conveyed to the brain by means of afferent fibers in the vagus nerve (Maier & Watkins, 1998).

The assumption that nervous, endocrine, and immune systems operate outside the reach of sociocultural influences allowed focused study of isolated anatomical systems. The advances resulting from such studies do not imply logically that social psychological or behavioral approaches have been eclipsed or are obsolete, however. Research that considers contextual and social factors has uncovered new effects that challenge some of the existing conceptualizations in the neurosciences. For instance, strains of mice with specific genes inactivated (i.e., knockout mice) have become important tools in biomedical research. Although the phenotypic expression of a knockout has been known to depend on the genetic background (see, e.g., Gerlai, 1996), the effects of the environmental context were thought to be unimportant. Crabbe, Wahlsten, and Dudek (1999), however, demonstrated that the specific behavioral effects associated with a given knockout varied across testing environments within and across laboratories. Crabbe et al. noted that the specific experimenters performing the testing were unique to each laboratory and could have influenced the behavior of the mice, concluding that

> for behaviors with smaller genetic effects (such as those likely to characterize most effects of a gene knockout), there can be important influences of environmental conditions specific to individual laboratories, and specific behavioral effects should not be uncritically attributed to genetic manipulations such as targeted gene deletions. (p. 1672)

As discussed below, the effects of social context also appear to be powerful determinants of the expression of autonomic, neuroendocrine, and immune reactions.

The documentation of associations between social and biological events does not prove that these events are causually linked, nor does it speak to the mechanisms underlying such effects. These are essential questions that need to be addressed, and we return to this issue in a later section. Generally speaking, however, the field is in a relatively embryonic stage with current knowledge about

underlying mechanisms woefully inadequate. As the 21st century begins, specialization is increasing within the biological and social sciences. Some in the neurosciences contend that psychological/behavioral approaches have been eclipsed, whereas some in the social sciences contend that biological approaches are irrelevant to an understanding of society and culture (see Berntson & Cacioppo, in press). It is not surprising in this context that some departments have become fractionated and that alternative organizations to the discipline of psychology have been offered (cf. Gazzaniga, 1998; Scott, 1991). One aim here is to review evidence for the importance of adopting complementary social and biological levels of analysis in the study of complex biobehavioral phenomena.

We focus on a few relatively well-developed fields of research in the area of health and disease. Within the normal range of human behaviors, social and biological approaches are also beginning to advance understanding of affect and emotions, attraction and sexuality, social development, and altruism and aggression. By way of background, however, we start with a brief discussion of why the social world could conceivably be central to understanding the biology of the mind and behavior.

The Centrality of Personal Ties and Social Interactions

Evolution has sculpted the human genome to be sensitive to and succoring of contact and relationships with others. People form associations and connections with others from the moment they are born. The very survival of newborns depends on their attachment to and nurturance by others over an extended period of time (see Baumeister & Leary, 1995). The human brain may have evolved to recognize human faces holistically (Farah, Wilson, Drain, & Tanaka, 1998). Distress vocalization, a signaling mechanism designed to solicit and sustain care, is one of the most primitive forms of audiovocal communication (Carden & Hofer, 1990; Panksepp, Herman, Conner, Bishop, & Scott, 1978). Language, the bedrock of complex social interaction, is universal and ubiquitous in humans. Even in the rare instances in which language is not modeled or taught to nonhearing children, a language system nevertheless develops (see, e.g., Goldin-Meadow & Mylander, 1983, 1984).

The need to belong does not stop at infancy; rather, affiliation and nurturant social relationships are essential for physical and for psychological well-being across the life span (see, e.g., Cohen & Syme, 1985; Gardner, Gabriel, & Diekman, 2000; Seeman, 1996). The handling of rat pups alters maternal behavior toward the pups and affects the structure and reactivity of the hypothalamic pituitary adrenocortical system (Meaney, Sapolsky, & McEwen, 1985). These early influences on the stress-hormone system, in turn, affect the pups' reactions to stressors and possibly their susceptibility to disease in later life (King & Edwards, 1999; Meaney et al., 1996). If these results generalize to humans, their theoretical and clinical implications are of significant import.

In humans, hormonal (see, e.g., Uvns-Mosberg, 1997) and neurophysiological substrates of caregiving and attachment have been identified (see Carter, Lederhendler, & Kirkpatrick, 1997). Consistent with animal research, the restriction of social contact during infancy and childhood has dramatic effects on psychopathology across the life span (Carlson & Earls, 1997). People who report having contact with intimate friends not only are more likely to report that their lives are very happy as compared with those who do not report such contact (Burt, 1986) but also tend to have lower blood pressure (see Uchino, Cacioppo & Kiecolt-Glaser, 1996). Disruptions of personal ties, whether through ridicule, discrimination, separation, divorce, or bereavement, are among the most stressful events people must endure (see Gardner et al., 2000).

The motivational potency of the absence of personal ties and social acceptance is reminiscent of more basic needs such as hunger. Solitary confinement is one of humankind's most severe punishments (Felthous, 1997). Ostracism, the exclusion by general consent from common privileges or social acceptance, is universal in its aversive and deleterious effects (Williams, 1997). Positively, tactile contact is a stronger determinant of mother–infant attachment than feeding (Harlow & Harlow, 1973). Subtle cultural influences can also rival more basic drives in governing feeding behavior and body weight (Becker, 1999).

Social and cultural influences not only cause behavior but alter biological processes as well. In such instances, a strictly physiological (or social) analysis is not sufficient to reveal the orderly relationships that exist, regardless of the sophistication of the measurement technology. For example, when Haber and Barchas (1983) investigated the effects of amphetamine on male Rhesus macaques, no clear contrast between the drug and placebo conditions was detected until each male's role in the social group was considered. When this social factor was taken into account, amphetamines were found to increase dominant behavior in males high in the social rank and to increase submissive behavior in low-ranking animals. Although, in retrospect, this pattern of data fits Hull-Spence drive theory in which arousal enhances habitual modes of response, the pattern became apparent only when considering the social and the biological contexts in which the behavior unfolds. The mechanisms underlying mind and behavior may therefore not be fully explicable by a biological or social approach alone; rather, a multilevel integrative analysis may be essential.

Social Influences on Genetic Constitution

In biology, the environment is seen as the agent of natural selection (Gottlieb, 1998). The notion that physical and social forces modulate gene frequency may therefore be regarded as uncontroversial. Mechanisms of selection may help explain otherwise perplexing demographic differences. For instance, the prevalence and incidence rates of hypertension, obesity, and Type 2 diabetes in immigrants from developing countries are substantially higher than in the majority population. Neel (1962) proposed the "thrifty gene" hypothesis—that across generations, individuals who were most likely to survive the hardship and food and water deprivation of developing countries inherited a gene (or set of genes) that conserved energy. Those who were constitutionally characterized by high insulin levels, low metabolism, high fat storage, and insulin resistance were more likely to survive these severe conditions. Migration from traditional lifestyles and environments to more sedentary lifestyles and calorie-dense environments has, therefore, been posited to increase the likelihood of obesity, Type 2 diabetes, and related diseases (see review by Osei, 1999). Such outcomes might be thought of as natural social (i.e., migratory patterns, lifestyle) and environmental (e.g., caloric density of the diet) influences on gene frequency in a population. The social forces operating as the agents of selection are not always so natural, however.

Wilson and Grim (1991) examined the historical record of the transatlantic slave trade and New World slavery from the 16th to 19th centuries to determine the circumstantial evidence for this reasoning (see also Anderson & Scott, 1999). More than 12 million young men and women were imported to the western hemisphere from Africa during the centuries of slave trade. Wilson and Grim estimated that the average mortality from capture to delivery on the West African coast was about 10%, mortality during confinement on the coast was about 12%, and mortality during the transatlantic passage was about 12%–15%. Of those who made it to the western hemisphere, 10%–30% were estimated to not have survived the first 3 years of slavery, and mortality rates remained high thereafter. Fertility rates of the survivors were low, and infant mortality rates may have been as high as 50%. It is at least plausible, therefore, that the transatlantic slave trade, which continued for centuries, imposed a strong selection pressure favoring specific biological mechanisms enabling survival and reproduction under the harsh conditions of slave trading.

Wilson and Grim (1991) further hypothesized that the specific biological mechanism underlying these effects was the set-point for salt regulation. The combined hardships of food and water deprivation and intense physical demands, Wilson and Grim suggested on the basis of historical records, resulted in a high proportion of deaths by volume depletion. Cholera pandemics also swept through the New World, killing thousands of slaves. This led Wilson and Grim to conclude that

> salt-depleting conditions and diseases seemed to be ubiquitous throughout the slavery period. . . . Individuals with an enhanced genetic-based ability to conserve salt (Na^+ conservers) would have a decided advantage over others under the severe salt-depletive conditions of slavery. (p. 1126)

Wilson and Grim's (1991) hypothesis is untestable, there is some uncertainty about the accuracy of their specific estimates, and the physical environment in West Africa during the 16th to 19th centuries may have been an important factor as well (see, e.g., Weder & Schork, 1994). It is nevertheless a provocative theory that has helped organize and explain some of the contemporary research on ethnic differences in hypertension (Anderson & Scott, 1999). Sodium intake results in cardiovascular volume expansion and an associated increase in arterial blood pressure, which triggers the kidney to increase sodium excretion until a new steady state is reached. If the kidneys retain more salt, a steady state is ultimately reached at a higher than normal blood pressure (Blaustein & Grim, 1991). If the high and nonrandom mortality rates that characterized the slave trade over 3 centuries resulted in a change in frequencies of specific genes—an increase in those favoring an elevated regulatory set-point for sodium balance—this could help explain why African Americans, relative to Whites, have higher rates of hypertension (see Anderson & Scott, 1999), greater sensitivity to increases in dietary salt (Luft, Rankin, et al., 1979), greater retention of an intravenous sodium load (Luft, Grim, Fineberg, & Weinberger, 1979), and better de-pressor responses to diuretics (Freis, Reda, & Materson, 1988).

Even here, though, the phenotypic expression of blood pressure is sensitive to social and environmental factors (Anderson & Scott, 1999; Grim et al., 1990; Light et al., 1995; Saab et al., 1997; Wilson, Hollifield, & Grim, 1991). In a study of 10,014 African Americans in Nigeria, Cameroon, Jamaica, St. Lucia, Barbados, and Chicago, for instance, Cooper et al. (1997) found that the prevalence of hypertension rose with urbanization. Specifically, mean arterial pressure was similar among young adults (aged 25–34), but the increase in hypertension prevalence with age was significantly steeper in the United States than in the Caribbean and twice as steep in the United States as in Africa. Stress on the job and lack of control in everyday life—features of urbanization—have been found to covary with elevated ambulatory blood pressure, increased left ventricular mass index, increased progression of atherosclerosis, and increased risk of coronary heart disease (Bosma et al., 1997; Schnall, Schwartz, Landsbergis, Warren, & Pickering, 1992).

As suggestive as these studies might be, none prove any necessary or causal influence between social factors and cardiovascular function. We therefore turn to the experimental literature on social factors and cardiovascular function.

Social Influences on Cardiovascular Function

Animal studies provide among the best experimental evidence for social influences on autonomic function and cardiovascular disease. In a series of studies in cynomolgus monkeys, for instance, Manuck, Kaplan and colleagues (e.g., Manuck, Marsland, Kaplan, & Williams, 1995; Skantze et al., 1998) demonstrated that social disruptions and instability promote coronary atherogenesis. Specifically, animals exhibiting a heightened cardiac reactivity to stress were found to develop the most extensive coronary lesions, whereas beta-adrenergic blockade—a pharmacological intervention that blocks the sympathetic activation of the heart—was found to prevent the behavioral exacerbation of atherosclerosis. To study the effects of a stressful social environment, social groups were repeatedly reorganized. Macaque males respond antagonistically to the presence of strangers and reassert their hierarchic relationships (Kaplan et al., 1982). Disruptions of social connections increased the formation of endothelial lesions even in the absence of an atherosclerosis-inducing diet (Kaplan et al., 1983), an effect that was again eliminated by beta-adrenergic blockade (see, e.g., Skantze et al., 1998). These results implicate the sympathetic nervous system in the etiology of behaviorally induced atherosclerosis.

The incidence of atherosclerosis is lower for premenopausal females than for similarly aged males, an effect found in humans and monkeys (cynomolgus macaques). Kaplan et al. (1984) found that premenopausal female monkeys developed significantly less coronary artery atherosclerosis than similarly housed males but only if the females were socially dominant. The mechanism underlying this effect is different for females than for males, however (Kaplan et al., 1996). Subordinate monkeys were found to have fewer ovulatory cycles, reduced levels of circulating estradiol, and altered luteal phase plasma progesterone concentrations. Ovariectomized females fed an atherogenic diet resulted in endothelial lesions in dominant females that were comparable to those found in reproductively intact subordinate females (Adams, Kaplan, Koritnik, & Clarkson, 1987). These results suggest that estrogen serves a protective function against atherosclerosis. In a subsequent study, subordinate premenopausal females and dominant females developed comparably low levels of atherosclerosis when fed an atherogenic diet and an oral contraceptive containing estrogen (ethinyl estradiol and levonorgestrel), relative to subordinate

females fed an atherogenic diet (Kaplan et al., 1995). These results suggest that social subordination impairs ovarian function, thereby potentiating atherosclerosis.

In both males and females in this research, high cardiovascular reactivity has been associated with increased risk for atherosclerosis. Light and colleagues have similarly focused on cardiovascular reactivity but have examined its relationship to hypertension and predisease indicators of hypertension such as left ventricular mass—essentially, the size of the muscle of the left ventricle of the heart (Hinderliter, Light, Girdler, Willis, & Sherwood, 1996; Light, Girdler, & Hinderliter, 2000). For instance, Hinderliter et al. (1996) found that the magnitude of blood pressure responses during laboratory stressors and natural life demands was a stronger predictor of left ventricular mass index and relative vascular wall thickness than either clinical blood pressure or baseline blood pressure. These and related studies by Light and colleagues indicate that cardiovascular responses to the demands of everyday life add prognostic information to that which can be obtained from clinical blood pressure levels (Light et al., 2000).

The risk of hypertension varies with family history. To test whether stress reactivity to the demands of everyday life would increase the risk of later blood pressure elevation in those individuals with a genetic susceptibility to develop hypertension, Light et al. (1999) conducted a 10-year follow-up study of 103 young men. Results revealed that men with a positive family history of hypertension had a twofold increase in risk of elevated blood pressure over 10 years as compared with men with a negative family history. However, men with a positive family history who also were in the top quartile in cardiovascular reactivity—as measured 10 years earlier—had a sevenfold increase in risk. In addition, high exposure to stress fostered increases in blood pressure at the follow-up in the high reactors. Importantly, it tends to be social stressors, not postural changes and exercise, that elicit these damaging cardiovascular reactions (Light et al., 1999).

The generalizability of the animal studies to humans can be questioned, and longitudinal research on the development or exacerbation of hypertension in humans has tended to use samples of convenience, is generally correlational, and typically relies on predisease markers or risk factors rather than disease end points. Rather than looking for increased blood pressure following social disruption, a handful of intervention studies exist with a complementing aim—to foster social support in an attempt to lower blood pressure in hypertensives. In a classic study, Levine et al. (1979) identified 400 hypertensive patients and assigned them to interventions consisting of an exit interview, family support, small group, various combinations of these three, or a control condition. In the family support intervention, for instance, patients identified an individual with whom they had frequent contact (e.g., spouse), and these individuals were trained to increase understanding, support, and reinforcement about the positive management of the patient's hypertension. Assessment at an 18-month follow-up indicated that family support was associated with an 11% decrease in diastolic blood pressure, and all of the interventions combined produced a 28% decrease. Subsequent follow-ups revealed that there were long-term benefits in blood pressure regulation as well (Morisky, DeMuth, Field-Fass, Green, & Levine, 1985). Meta-analyses of this and related studies confirmed that increases in social support resulted in decreased blood pressure in hypertensive patients (Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Together, studies of social influences on cardiovascular function suggest substantial plasticity in the relationship between genetic factors and the development of cardiovascular disease.

Social Influences on Genetic Expression

As noted above, a central precept of molecular biology is that all the information needed to construct a mammalian body, whether human or mouse, is contained in the approximately 100,000 genes of mammalian DNA and that a set of master genes activates the DNA necessary to produce the appropriate proteins for development and behavior (Crick, 1970; Panksepp, 1998). Our thesis in this article is that the social world, as well as the organization and operation of the brain, shapes and modulates genetic and biological processes, and accordingly, knowledge of biological and social domains is necessary to develop comprehensive theories in either domain. In this section, we review evidence that some aspects of genetic expression that had been thought to be encapsulated within each living cell far from the reach of personal ties or social influences are in fact subject to modulation by the social environment (see Gottlieb, 1998).

In broad brush strokes, DNA encodes the sequence of amino acids in proteins and peptides by the sequence of nucleotides in the gene. By means of the process of transcription, involving RNA polymerases (enzymes), this sequential code is transferred to messenger RNA (mRNA), followed by translation to polypeptide chains and proteins. Recent research on the control of the secretion of lymphocyte growth hormone (L-GH) by peripheral blood mononuclear cells indicates that the social world can modulate transcription processes (as reflected in differences in mRNA levels). Briefly, Wu, Devi, and Malarkey (1996) localized (by in situ hybridization) growth hormone messenger RNA (GH mRNA) in human immune organs, including the thymus, lymph nodes, spleen, and peripheral blood, as well as in thymomas and lymphomas. The extant literature on growth hormone suggests that it can influence cellular immunity by altering the efficacy of lymphocytes in responding to antigens (Wu et al., in press). The genetic transcriptions responsible for the production of L-GH are in part predetermined, as evidenced by the robust finding that L-GH secretion decreases with aging. However, Malarkey et al. (1996; Wu et al., in press) also found evidence for the modulation of L-GH levels by social stressors. Specifically, caregivers of spouses with Alzheimer's disease were found to have markedly suppressed L-GH concentrations compared with age- and gender-matched controls. Although more research is needed to specify the mechanism by which the social world modulates GH mRNA, stress hormones such as adrenocorticotrophic hormone, cortisol, and catecholamines appear to play a role through their regulatory effects on lymphocytes.

The social influence on phenotypic expression is also illustrated in recent research on early nurturance. Suomi (1999) selectively bred Rhesus monkeys to produce offspring who, on the basis of their genetic pedigree, were either normally or highly reactive to stressors. These selectively bred infants were then cross-fostered to unrelated multiparous females who were either normally or unusually nurturant with respect to attachment-related behavior. The infants were reared by their foster mothers for the first 6 months of life and were then placed in a larger social group containing age-mates who were cross-fostered or were raised by their biolog-

ical mothers (Suomi, 1987). Genetically high-reactive infants raised by normal (i.e., highly reactive) females showed the typical deficits in early exploration and accentuated responses to mild stressors, relative to genetically high-reactive infants raised by especially nurturant females. These latter infants explored their environments more and showed as little disturbance to mild stressors as, or lower levels than, their genetically high-reactive counterparts who were fostered by normal rather than nurturant mothers. Behavioral differences among these groups persisted when these monkeys were permanently separated from their foster mothers and were placed into a larger social group at 6 months of age (Suomi, 1991). Although the results are preliminary, Suomi (1999) reported that the serotonin transporter gene (5-HTTT)—and specifically, a 5-HTTT polymorphism, LS (short) vs. LL (long) 5-HTT allele—may be involved. Bennett et al. suggested that relatively nurturant mothering may buffer the deleterious developmental effects of the LS allele on serotonin metabolism and aggression.

Studies of rodents and monkeys have found that genetically highly reactive females also exhibit aberrant patterns of maternal care. For instance, Fischer rats are characterized by high hypothalamic–pituitary–adrenal (HPA) reactivity to stressors, whereas Lewis rats are characterized by low HPA reactivity. Accordingly, the Fischer rats have a lower threshold for stress reactions and show larger responses to stressors than Lewis rats. Fischer and Lewis dams also differ in their attention to and nurturance of their pups, with Fischer dams being much less attentive and nurturant even in the absence of an explicit stressor (Gomez, Riley, & Sternberg, 1997). A similar difference in maternal care has been observed in Rhesus monkeys (see, e.g., Suomi & Levine, 1998). Early nurturance appears capable of modifying this genetic predisposition, however. Suomi (1999), for instance, reported that genetically reactive females raised the first 6 months of life by an unusually nurturant mother "adopted the general maternal style of their foster mothers, independent of both their own original reactivity profile and the type of maternal style shown by their biological mothers" (p. 193).

Research on rats further suggests that early tactile deprivation reduces the number of glucocorticoid receptor binding sites in the hippocampus and frontal cortex by means of an action on gene expression (Meaney et al., 1985). Studies of rat pups indicate that transient early-life stress (e.g., brief handling) attenuates the behavioral and neuroendocrine responses to stressors encountered in adulthood, whereas early-life exposure to more severe stressors (e.g., protracted separation from the dam) accentuates responses to stressors in adulthood (Anisman, Zaharia, Meaney, & Merali, 1998). These effects appear to be mediated by variations in maternal care. Specifically, the brief handling of rat pups leads to greater maternal nurturance, increased glucocorticoid receptor binding sites in the hippocampus and frontal cortex, and lowered HPA reactivity in adulthood, whereas severe early-life stress has the opposite effects (Anisman et al., 1998; Meaney et al., 1993). Interestingly, as adult rats, the offspring of mothers that exhibited more licking and grooming and nurturance of pups during the first 10 days of life were not only characterized by reduced adrenocorticotropic hormone and corticosterone responses to acute stress but also, as mothers, tended to lick and groom their pups more (Liu et al., 1997).

Additional studies on the social influence of genetic expression are reviewed in the next section on psychoneuroimmunology. Together, these studies clearly illustrate synergistic influences between the social and biological levels of organization. The specific genes or social factors that interact may differ across species, but given the importance and complexities of genotypes and social factors in humans, the short-term and long-term modulation of genetic expression by social factors is almost certainly important to consider if a comprehensive model of human nature is to be developed. In monkeys, rats, mice, and humans, developmental processes and long-term health are not fully comprehensible if limited solely to either the social or the biological level of analysis.

Social Influences on Immune Activity

Empirical observations of social influences on autonomic activity date back more than 2,000 years (Mesulam & Perry, 1972). Until recently, however, immune functions were thought to reflect specific and nonspecific physiological responses to pathogens or tissue damage. It is now clear that the immune system is tightly regulated and integrated with the nervous and endocrine systems and that social events influence immune function through these systems. As noted above, a bidirectional communication network composed of soluble ligands and cellular receptors links both afferent and efferent limbs of the immune system to the nervous and endocrine systems. Thus, a stimulus within the nervous system that activates the sympathetic adrenomedullary (SAM) and HPA axis results in peripheral release of catecholamines and adrenal steroids, respectively, that have immunoregulatory potential. Similarly, a challenge within host tissue that induces an inflammatory response (e.g., an infection or a wound) results in the release of cytokines that stimulate peripheral and central circuits of the nervous system. This communication provides an important link through which the neuroendocrine response modulates the development of an inflammatory response at a site of challenge (Kusnecov, Liang, & Shurin, 1999; Maier & Watkins, 1998).

This communication system appears to be tuned, presumably by direct sympathetic innervation and circulating neuroendocrines, to social interactions, as well as to pathogens and tissue damage. Persons in marital conflict (see, e.g., Kiecolt-Glaser et al., 1987), taking important examinations (see, e.g., Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984), and living near the site of a serious nuclear-power plant accident (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989) have been found to show diminished immune function on quantitative and functional measures. Clinical depression (Herbert & Cohen, 1993a) and psychological distress (Herbert & Cohen, 1993b) have also been associated with decreased immune function. Small immunological decrements do not necessarily indicate poorer health status or risk for disease among young and healthy adults, however. Studies of the effects of psychosocial stress on vaccine responses have therefore been conducted to help address this criticism (see Glaser, Rabin, Chesney, Cohen, & Natelson, in press). Using the stress of taking a university examination (Glaser et al., 1992) or the chronic stress of being a caregiver (Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996), Glaser and colleagues found that the response to vaccination was diminished in high- compared with low-stress conditions. Because

respiratory and viral infections remain a major cause of morbidity and mortality among older adults (McGlone & Arden, 1987), the differences in immune response to influenza virus vaccination in the elderly were thought to have health significance (Glaser et al., in press).

Another arena of research that has emerged in part to improve experimental control and in part to address the health relevance of the changes in immune function found in psychoneuroimmunological studies is wound healing. An individual is protected from infection following wounding by the rapid reestablishment of the barrier provided by intact mucosal surfaces or skin. This process is orchestrated by early inflammatory responses that include proinflammatory cytokines (e.g., IL-1 and TNF), chemokines (e.g., IL-8, MCP-1, and MIP-1α), and growth factors (e.g., keratinocyte growth factor and vascular endothelial growth factor). Consequently, the speed and completeness of wound healing has health relevance (Marucha, Kiecolt-Glaser, & Favagehi, 1998). Perhaps more importantly, the wound-healing paradigm affords greater experimental control over individual differences and spurious behavioral and contextual factors in human studies. For instance, Kiecolt-Glaser and colleagues examined wound healing and the immunological responses contributing to this end point in spousal caregivers of patients with Alzheimer's disease and age- and gender-matched controls (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995) and in dental school students when they were or were not undergoing exams (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998; Marucha et al., 1998). In both models, higher levels of stress were associated with delayed wound healing.

If social disruptions are transduced to the level of regulation of gene expression, it is conceivable that the expression of host resistance genes (encoded within the cells of the immune system) can also be modulated by social disruption. To test this hypothesis, Padgett and Sheridan (1999) developed an experimental model in which they explored the biological effects of reorganizing established murine (mouse) hierarchies during a respiratory viral infection. Results revealed that social disruption led to significantly higher mortality due to viral infection than found in home-cage control animals (Padgett & Sheridan, 1999). Further analyses revealed that the increased severity of the infection leading to mortality was associated with the development of hyperinflammatory responses due to overexpression of key cytokine genes. The increased cell trafficking and accumulation in the lungs of infected animals led to tissue consolidation or congestion and, consequently, to diminished lung function. Importantly, a different result was found for nonsocial stress (i.e., physical restraint). The physical restraint paradigm is devoid of social interactions but activates the HPA axis in a fashion similar to the psychosocial stressor. Thus, physical restraint is as stressful to the animal as social disruption, but the stressor is centered on the animal's interaction with the physical rather than the social world. In physical restraint, hypo-inflammatory (rather than hyperinflammatory) responses were observed during respiratory viral infection in these animals, due to suppression of cytokine responses by glucocorticoid hormones. Consequently, the observed rate of mortality was much lower in these infected animals than in those who were infected and exposed to social disruptions.

The social ordering within social hierarchies may also play a role in the individual responses to psychosocial stress and susceptibility to infectious disease. For instance, in the social disruption paradigm, dominant male mice, when latently infected in the trigeminal ganglia with herpes simplex virus (HSV; a model for recurrent herpes labialis in humans), were twice as likely as subordinate animals to reactivate and shed infectious virus when their social environment was disrupted by reorganization (Padgett, Sheridan, et al., 1998). The psychosocial nature of the stressor was again important, as simply stressing latently infected mice by physical restraint did not cause reactivation (Padgett, Sheridan, et al., 1998).

The key finding of these experimental studies is that social interactions influenced physiological signals that modulate the expression of individual host/pathogen genes. In the model of latent HSV infection, the inactive viral genome represents an environmental (or foreign) gene that has parasitized the host. It resides in the neurons of the trigeminal ganglia and remains latent or inactive until an appropriate set of physiological signals is received. Although the reason is not entirely understood yet, psychosocial stress provided the appropriate set of signals for reactivation of the viral genes leading to recurrent infection and the shedding of infectious virus (Padgett, Sheridan, et al., 1998).

The focus in these studies is on the immunosuppressive effects of stress, but acute stressors can also facilitate the development of localized immunity by causing cells of the immune system, such as lymphocytes and macrophages, to redistribute throughout the body (Dhabhar & McEwen, 1997; Dhabhar, Miller, McEwen, & Spencer, 1995; see also Uchino, Cacioppo, Malarkey, & Glaser, 1995). Immune cells marginate on blood vessel walls and traffic or localize within the skin, lymph nodes, and bone marrow (Dhabhar et al., 1995). It has been suggested that the regional positioning of these immunocytes (in response to acute stress) may provide the host with a selective advantage should aggressive behavioral interactions lead to cutaneous wounding and the possibility of infection (Dhabhar & McEwen, 1997). The selective advantage that may accompany acute stress does not extend to chronic forms of stress, however, as the prolonged activation of the HPA axis and sympathetic nervous system seen in chronic stress tends to suppress cellular immunity (Lupien & McEwen, 1997; Sheridan, 1998), reduce response to vaccination (Kiecolt-Glaser et al., 1996), and slow the healing of experimental cutaneous and mucosal wounds (Kiecolt-Glaser et al., 1995; Marucha et al., 1998; Padgett, Marucha, & Sheridan, 1998). Accordingly, it is the prolonged activation of the HPA axis and sympathetic nervous system that is thought to underlie the disruption of normal immune functioning by chronic family or job strain, although this is almost certainly an incomplete answer.

Social Influences on Disease

One implication of the research reviewed thus far is that the development and progression of disease, once bastions of the biological approach, may be influenced dramatically by social factors (Anderson, 1998). Epidemiological research has indeed marshaled evidence for a strong relationship between health and various social circumstances (see, e.g., Adler et al., 1994; Carroll & Sheffield, 1998; Kitagava & Hauser, 1973; Rogot, Sorlie, Johnson, & Schmit, 1993; Townshend & Davidson, 1982). In a classic study, Berkman and Syme (1979) operationalized social connections as marriage, contacts with friends and extended family mem-

bers, church membership, and other group affiliations. They found that adults with fewer social connections suffered higher rates of mortality over the succeeding 9 years even after accounting for self-reports of physical health, socioeconomic status, smoking, alcohol consumption, obesity, race, life satisfaction, physical activity, and preventive health-service usage.

House, Robbins, and Metzner (1982) replicated these findings using physical examinations to assess health status. In their review of five prospective studies, House, Landis, and Umberson (1988) concluded that social isolation was a major risk factor for morbidity and mortality from widely varying causes. This relationship was evident even after statistically controlling for known biological risk factors, social status, and baseline measures of health. The negative health consequences of social isolation were particularly strong among some of the fastest growing segments of the population: the elderly, the poor, and minorities such as African Americans. The strength of social isolation as a risk factor was comparable to high blood pressure, obesity, sedentary lifestyles, and possibly even smoking. House et al. (1988) concluded that

> the mere presence of, or sense of relatedness with, another organism may have relatively direct motivational, emotional, or neuroendocrinal effects that promote health either directly or in the face of stress or other health hazards but that operate independently of cognitive appraisal or behavioral coping and adaptation. (p. 544)

A meta-analytic review of the experimental literature revealed that perceived social isolation was associated with physiological adjustments, with the most reliable effects found for blood pressure, catecholamines, and aspects of both cellular and humoral immune function (Uchino et al., 1996; see also Seeman & McEwen, 1996). These results could not be explained entirely in terms of existing individual differences because intervention studies designed to reduce social isolation improved physiological functioning (Uchino et al., 1996). People's perceptions of others in light of their desire for affiliation appear to be important, too, as subjective indices of social isolation/support have been found to be more powerful predictors of stress and health than objective indices (see Seeman, 1996; Uchino et al., 1996).

Although individual differences and differences in health behaviors may contribute to health outcomes, social isolation and stress appear to diminish health by means that are not yet fully understood. Cohen, Tyrrell, and Smith (1991), for instance, tested 420 healthy volunteers, measured their level of stress (e.g., perceived stress, major life events), and exposed them to saline or one of five different strains of Rhinoviruses, to a strain of coronavirus, and to respiratory syncytial virus. Following inoculation, participants were quarantined and monitored for the development of disease. After 7 days of quarantine, each participant was classified as not infected, infected but not ill, or infected and ill. No participant who was exposed to saline became ill, and about a third of the participants exposed to the cold viruses became ill.

Three measures of stress were related to disease onset: a stressful-life-event scale to measure the cumulative event load, a perceived-stress scale to assess perceptions of overload-induced stress, and a measure of negative affect. For each measure, participants were categorized as under high or low stress according to whether their score on each scale fell above or below the median score. For all three measures, participants who reported high stress were more likely to develop an infectious disease than those who reported low stress. In a follow-up study, Cohen et al. (1998) used an interview to determine the type of stressors that increased susceptibility for disease. Results revealed that risk was increased most by stressors lasting over a month, especially social conflicts, unemployment, and underemployment. The effect appears to be replicable; more research is now needed to delineate the mechanism underlying these findings.

The research by Cohen and colleagues also suggests that close relationships are not uniformly positive or salubrious. Indeed, results from the Terman Life Cycle Study indicate that past negative behaviors in social relationships are associated with greater mortality (Friedman et al., 1995; Tucker, Friedman, Wingard, & Schwartz, 1996). Laboratory research has found that negative or hostile behaviors during a marital conflict produce greater and/or more persistent alterations in autonomic activation (Gottman & Levenson, 1992; Levenson, Cartensen, & Gottman, 1994) and circulating stress hormones (Kiecolt-Glaser, Malarkey, Cacioppo, & Glaser, 1994; Kiecolt-Glaser et al., 1997). Moreover, couples characterized by high, relative to low, negative behaviors during a marital conflict also showed greater decrements in cellular immune function over the 24 hours of study (e.g., natural killer-cell lysis, the blastogenic response to two mitogens, the proliferative response to a monoclonal antibody to the T3 receptor; Kiecolt-Glaser et al., 1994). In a cross-sectional study of young and older adults, Uchino, Holt-Lunstad, Uno, and Flinders (1999) found that high ambivalence was associated with increasing levels of depression and cardiovascular reactivity as a function of age. As in the animal studies, studies of humans suggest that feeling embattled or feeling isolated can have deleterious health consequences. Sympathetic hyper-reactivity (see, e.g., Uchino et al., 1996) and elevated HPA activation (see, e.g., Cacioppo et al., in press) may be especially fruitful candidates for study as mediators between social disruptions and disease.

Multilevel Integrative Analyses

The Decade of the Brain has led to a realization that a comprehensive understanding of the brain cannot be achieved by a focus on neural mechanisms alone, and advances in molecular biology have made it clear that genetic expressions are not entirely encapsulated, that heritable does not mean predetermined. A social or behavioral level of analysis is also insufficient, of course. Social processes and behavior are profoundly affected by brain injury, as documented in cases such as that of Phineas Gage (Damasio, 1994; Macmillan, 1986). Phineas Gage was a railway worker who was described as an exemplary citizen, energetic, shrewd in personal and financial affairs, and persistent. At work one day, he accidentally ignited an explosive charge, driving his tamping iron through his skull and ravaging the ventromedial aspects of the most anterior portions of the frontal cortex in the left and right hemispheres. Gage's personality changed permanently and profoundly following the accident. He became profane, impatient, capricious, and impulsive, as well as given to outbursts of anger and rage. The social relationships that existed prior to the accident deteriorated thereafter.

Individuals who lose the amygdala and associated inferior portions of the temporal cortex exhibit another disruption of social propriety known as the Kluver-Bucy syndrome (Kluver & Bucy, 1939). These individuals are characterized by a loss of fear and

increased and inappropriate sexual activity. Prosopagnosics, who typically have bilateral lesions in the occipital lobes near the temporal lobes, do not undergo a change in personality but have another disturbing problem that alters their social behavior: They no longer recognize the faces of those they once knew (e.g., spouses) even though they show larger skin conductance responses to familiar faces (Tranel, Fowles, & Damasio, 1985). Interested readers should see Klein and Kihlstrom (1998) for a recent review of this literature, but the examples here illustrate that everyday social behaviors such as sexuality, decorum, aggression, altruism, conformity, and social influence are quintessentially social and neurophysiological processes.

Several general principles may help organize research in this area (Anderson, 1998; Cacioppo & Berntson, 1992b). First, the principle of multiple determinism specifies that a target event at one level of organization—particularly at molar (e.g., social) levels of organization—may have multiple antecedents within or across levels of organization. Eating, for instance, is influenced by both hunger and social cues (Cornell, Rodin, & Weingarten, 1989).

The principle of nonadditive determinism specifies that properties of the whole are not always readily predictable from the properties of the parts (Cacioppo & Berntson, 1992b). This principle is evident in a study of male mice infected intranasally with a respiratory virus (Padgett & Sheridan, 1999). One group was left in their home cage (five mice per cage), a second group was exposed to 12 hrs of daily restraint stress, and a third group underwent social reorganization (dominant animal shifted to new cage on Days -3, -1, $+1$, and $+3$ of infection). Corticosterone levels were equally elevated in the stressed groups, relative to the control group. Within 8 days of the infection, however, approximately 8% of the control group died, 15% of the restraint stressed group died, and 70% of the socially stressed group died (Padgett & Sheridan, 1999). The order in these data is not fully comprehensible at any one level of organization but instead emerges when viewed across social and biological levels of analysis.

Associations do not imply causation, but often, the causal direction that is tested depends on one's disciplinary level of analysis. The principle of reciprocal determinism specifies that there can be mutual influences between microscopic (e.g., biological) and macroscopic (e.g., social) factors in determining behavior (Cacioppo & Berntson, 1992b). For example, not only has the level of testosterone in nonhuman male primates been shown to promote sexual behavior but also the availability of receptive females influences the level of testosterone (Bernstein, Gordon, & Rose, 1983; Rose, Gordon, & Bernstein, 1972). Zillmann (1984) has demonstrated that exposure to violent and erotic materials influences the level of sympathetic arousal in male humans, and that the level of arousal has a reciprocal influence on the perceptions of and tendencies toward sex and aggression. A low-reactive HPA system produces an adult rat who is low in stress reactivity, who is attentive to offspring, and who frequently licks and grooms the offspring. Licking and grooming, however, are essential for the offspring to develop into a low-reactive adult who frequently licks and grooms offspring (Liu et al., 1997). Given the reciprocal influences between social and biological processes, comprehensive accounts of these behaviors will remain elusive as long as either biological or social levels of organization are considered unnecessary or irrelevant.

In writing about unhealthy environments, Taylor, Repetti, and Seeman (1997) articulated a general framework for thinking about how social factors penetrate the skin. Although Taylor et al. focused on the effects of race and social class on health, the routes are applicable generally to the question of how other social factors get under the skin. These routes, although distinguishable, are not mutually exclusive.

The first route emphasizes the cumulative effects of chronic or repeated stressors. Primary caregivers for spouses with dementia, who are subject to years of daily physical and social stressors, also show poorer immunosurveillance (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991) and elevated sympathetic cardiac tonus (Cacioppo et al., 1998) than matched controls. Studies of the cumulative effects of stressors on biology and health have led to the concept of allostatic load (McEwen & Stellar, 1993). Sterling and Eyer (1988) introduced the term allostasis to capture the complexities of visceral regulation, particularly the effort required to maintain a highly regulated state in a complex system. Like Selye (1973), these authors recognized that regulatory levels are not fixed but may be flexibly adjusted to meet changing demands. The allostatic concept recognizes that many visceral dimensions are regulated by multiple, interacting mechanisms and that these mechanisms are subject to a broader range of modulatory influences, whether derived from exogenous challenges or natural endogenous processes. These adjustments are seen as reflecting the adaptive readjustment of regulatory levels, given changing physiological demands (Berntson & Cacioppo, in press). Over time, however, the physiological costs of these adjustments (i.e., the allostatic load) build up, culminating in cumulative identifiable damage that results in increased pathology (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). The heightened, repeated, or extended activation of the SAM and HPA axes and the concept of allostatic load are thought to play a role in several of the routes outlined below, as well.

A second route by which social factors may affect biology and health is by means of their impact on affective processes (e.g., distress) and mental health (Taylor et al., 1997). The anxiety, hostility, and depression that characterize lonely individuals, for instance, represent a constellation of psychological traits that has been linked to maladaptive coping, increased stress reactivity, and all-cause mortality (see, e.g., Booth-Kewley & Friedman, 1987; Martin et al., 1995). Hostility, distress, depression, and negativity more generally have been linked to alterations in the activation of both the SAM and the HPA systems, with consequent effects on cardiovascular disease (see, e.g., Krantz & Manuck, 1984; Manuck et al., 1995; Troxler, Sprague, Albanese, Fuchs, & Thompson, 1977) and immune function (see, e.g., Cohen & Herbert, 1996).

A third route by which social factors may have adverse health effects is through their impact on beliefs and attitudes about oneself (e.g., self-esteem), one's life (e.g., life satisfaction), one's future (e.g., hopefulness), or one's purpose in life (e.g., religiosity). In a remarkable study of the power of beliefs on health, Phillips, Ruth, and Wagner (1993) compared the deaths of 28,169 adult Chinese Americans with those of 412,632 randomly selected, matched Caucasian controls. Chinese astrology specifies that a person's fate is influenced by his or her year of birth. When people who believe in Chinese astrology contract a disease that is associated with the phase of their birth year, they are more likely than others to feel helpless, hopeless, or stoic. Phillips et al. reasoned,

therefore, that if these beliefs influenced biological processes and health, then Chinese Americans who have a combination of a disease and a birth year that Chinese astrology regards as ill-fated should be more likely to die significantly earlier than matched Caucasians. Results confirmed this prediction and further revealed that the more strongly a group was attached to Chinese traditions, the more years of life were lost. These effects were found for nearly all major causes of death.

A fourth and related route is the effects of coping strategies (Taylor et al., 1997). Research by Scheier et al. (1989) on recovery from coronary artery bypass surgery, for instance, demonstrated that optimism was associated with better coping efforts and surgical outcomes. Specifically, optimism was associated with more problem-focused coping and less denial, as well as faster rates of physical recovery during hospitalization and faster returns to normal activities following discharge. In a related line of research, Greenberg, Wortman, and Stone (1996) conducted a follow-up to research by Pennebaker and colleagues (e.g., Pennebaker, Kiecolt-Glaser, & Glaser, 1988) on the health benefits of personal disclosures and demonstrated that disclosing imaginary traumas had comparable health benefits to personal disclosures, a result they attributed to the enhancement of self-efficacy from the imaginal enactment of competent coping efforts.

Fifth, social factors may have an impact on biology and health through their influence on health habits and behaviors. Taylor et al. (1997; see also Adler & Matthews, 1994) reviewed recent evidence linking smoking, substance abuse, diet, exercise, adherence to treatment recommendations, and the use of preventive and secondary health services to the development of chronic diseases. Social isolation may be associated with higher rates of morbidity and mortality (House et al., 1988), for instance, because lonely individuals perform more health-endangering behaviors (smoking, alcohol or drug abuse, risk-taking actions; Cohen, 1988), engage in less frequent or effective recreational or restorative activities that counteract the typical effects of daily hassles and stresses (e.g., exercise, sleep, relaxation, eating nutritious meals; see, e.g., Umberson, 1987), or benefit less from salubrious behaviors such as sleep (Cacioppo et al., in press).

A sixth and related route, and one that can clearly coexist with others, is individual differences (cf. Uchino et al., 1996). Intelligent, optimistic, attractive people may tend to make better career and life decisions, have more options, and enjoy better health. Individuals high on hostility or neuroticism, in contrast, may have relatively negative social interactions, higher allostatic load, and poorer health. Indeed, personality factors such as neuroticism and extraversion appear to have large (and contrary) effects especially on subjective measures of health, such as self-reported symptomatology (Watson & Pennebaker, 1989). Schmidt et al. (1997) found that children who, at 4 months of age, displayed a high frequency of motor activity and negative affect (i.e., behaviorally inhibited temperamental pattern of behavior), in contrast to other 4-month-old infants, were described at 4 years of age by their mothers as being more shy. In addition, 4-year-olds who were characterized by a higher frequency of wary behavior during peer play also exhibited relatively high morning salivary cortisol, were reported as contemporaneously shy by their mothers, and had been behaviorally inhibited at 14 months of age. Schmidt et al. suggested that high levels of cortisol in these children may induce changes in the amygdala, exacerbating their fearfulness. Research is needed to examine the interface between social and personal factors, especially in reference to biology and health (McGonigle, Smith, Benjamin, & Turner, 1993; Uchino et al., 1996).

Finally, social isolation can lay the initial groundwork for a direct health effect (Taylor et al., 1997). Gurley, Lum, Sande, Lo, and Katz (1996), for instance, conducted a population-based study of patients who were found in their homes either helpless or dead. The median age of such persons was 73 years (51% women), with the frequency of such incidents rising sharply with age, in large part because these individuals were more likely to be living alone and, hence, were more vulnerable when a health problem arose.

These mechanisms have been difficult to examine for various reasons. First, these explanations, although distinguishable, are not mutually exclusive. Social behavior is multiply determined, as is likely are the means by which social factors have an impact on biology and health. Investigations of individual mechanisms in isolation, therefore, may hinder discovery of associations and interactions among these mechanisms. Furthermore, the routes outlined above need not be orthogonal. For example, an individual's beliefs and expectations may shape his or her appraisals, which in turn may influence the individual's affective reactions or health behaviors. Parsing the relative influence of these mechanisms requires multidisciplinary research drawing from expertise across multiple levels of organization. Traditionally, most laboratories and funding opportunities have supported single or very limited levels of analysis.

Second, the effect of social relationships on physiological responses has typically been studied in the laboratory. This makes it possible to rigorously examine specific constructs such as differential reactivity—the differences in the magnitude of a response to a given stimulus as a function of social processes (e.g., cardiovascular responses in individuals low vs. high in hostility). The extent to which these laboratory snapshots generalize to what people do or how they actually respond in their daily lives is an open question, however, one that advances in ambulatory recording procedures and experience sampling methods now make it possible to address (cf. Guyll & Contrada, 1998). The problem is not simply one of generalizability, either. The reactivity measured in the laboratory may generalize to everyday life, yet the effect may manifest not in differential reactivity but rather in differential exposure. Hostile individuals, for instance, may differ in the situations (e.g., social stressors or conflicts) they encounter or create rather than in the magnitude of their reactivity to a given stressor. Thus, both laboratory and field research may contribute to our understanding of the means by which the social world gets under the skin.

Third, cross-sectional studies in the area have relied primarily on self-reports to assess people's social construals and activities. It is imperative to consider the extent to which these data are reliable and valid descriptions of their social world, mean the same thing across groups of individuals (e.g., gender, ethnicity), and capture the important states of mind (see, e.g., Bradburn, Rips, & Shevell, 1987). Specific distortions in the retrospective verbal reports of stressful or emotional events, for instance, have been documented (Redelmeier & Kahneman, 1996).

Fourth, the prior research that has been conducted in the field has been almost exclusively correlational, leaving open the question of causal factors. Animal studies offer a valuable complement, although the generalizability of the results to humans is an issue

that must be considered. Nevertheless, one of the greatest challenges is to go beyond correlational data to reveal the psychological and physiological mechanisms involved. Longitudinal studies that span several levels of analysis may contribute to this end.

Finally, scientific inquiries require that individual investigators specialize and focus. Interdisciplinary research teams provide a means of overcoming this limitation, but disciplinary training and departmental reward contingencies tend to foster parochialism and work against the establishment of such teams. Parochialism, however, ignores the distinction between levels of explanation, the organization in the data that may become evident from research across levels of organization, the theoretical insights about the nature and timing of the relationships among variables that can be derived from descriptions of phenomena from multiple scales or perspectives, and the economy of thought that can be gained by using the form of representation most appropriate for the task. It also alienates scientists working at a different level of organization who might otherwise contribute relevant theory and data and renders it acceptable to ignore relevant research simply because it was not born from one's own level of analysis. Given that there are phenomena deriving from events at one level of analysis that are only or distinctly observable at other or broader levels of analysis, multilevel integrative analyses may contribute to the empirical data and theoretical insight needed for a comprehensive understanding of human behavior.

Conclusion

The complementarity of biological and social approaches to human behavior were not readily apparent when research methods were limited primarily to descriptions of the behavior of animals far removed from their ecological or evolutionary context, observations of patients who suffered trauma to or disorders of localized areas of the brain, and postmortem examinations. As a consequence, biological approaches tended to be viewed by social psychologists as uselessly reductionistic, whereas social approaches tended to be viewed by biopsychologists as more literary than scientific, more a history of human experience than a rigorous, robust, and replicable body of scientific knowledge (see Allport, 1947). Technical and methodological developments now enable biological measures of ongoing human behavior, including electrophysiological recording, functional brain imaging, and neurochemical techniques. Conversely, social methods for studying behavior and ambulatory recordings of biological function can now be applied to animals and humans living in complex environments, providing a more fruitful model for the dynamic interaction between biological mechanisms and social context. New disciplines have also emerged—genetics, molecular biology, neuroendocrinology, social neuroscience, and psychoneuroimmunology—along with techniques sufficiently refined that they can now be used together to elucidate the reciprocal interactions between neural and social processes. Changes in medical science, worldwide health problems (e.g., AIDS, chronic disease), and U.S. demographics have helped fuel basic social and biological research on societal problems. With both means and motive now available, there is growing evidence that a more comprehensive understanding of the mind and behavior will be fostered by integrative, theoretical analyses that span the biological and social levels of organization.

In sum, social and biological approaches are complementary rather than antagonistic. Together, these perspectives are helping to illuminate questions ranging from the social sciences to the neurosciences by examining how organismic processes are shaped, modulated, and modified by social factors and vice versa. Rather than viewing social psychology and biological psychology as generating inevitably oppositional forces that are ripping apart psychology departments (Scott, 1991), we see the potential for strong centripetal forces generated by research cutting across these distinct but equally important levels of organization.

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