Combinations of environmental stress coordinately increase toxicological assaults on health, dependent on the genetics of the exposed organism. Multiple gene variances between individuals influence the risks associated with environmental exposures, and environmental stress presents in multiple forms including chemical, physical, and psychological stresses. Combined chemical, physical, and psychological stresses are suggested as exacerbating the initiation and/or duration of illnesses, and many of the detrimental outcomes on health are posited to relate to changes in neuroendocrine immune circuitry. However, most human epidemiological or experimental animal studies have not considered the combination of chemical, physical, and psychological stress on health status. Current consideration is being given to “real world” exposures for assessment of health risk, but this mainly relates to evaluation of chemical mixtures. In addition to concomitant chemical exposures having agonistic and/or antagonistic interactions, the physical and psychological status of the individual can influence exposure outcomes. An individual’s psychosocial environment is likely to be important in epidemiological investigations. Neuroimmunology is a burgeoning discipline, and neurotoxicology and immunotoxicology studies should consider the bidirectional regulatory mechanisms between these organ systems and the potential long-term influences of psychological stress. This mini-review discusses some intriguing data from animal and human studies, which address the regulatory pathways between the neural, endocrine, and immune systems, with emphasis on psychological stress.

Behavioral, neurochemical, and immunological effects of environmental toxicants are well documented in both human epidemiological studies and experiments with laboratory animals. In general, these studies have focused on dose effects as well as on the impact of chemical mixtures. Less studied, however, are potential interactions between toxicant exposure and the psychological state of the exposed organism. Consideration of such interactions may be critical in addressing problems of illness associated with particular populations, such as individuals of lower socioeconomic status (SES), who are suggested to be at increased risk of illness (Adler and Ostrove, 1999; Breeze et al., 2001; Marmot et al., 2001). Undoubtedly, low SES is associated with greater likelihood of exposure to toxicants (e.g., lead-contaminated paints) and allergens as well as a greater number of physical stressors in the form of poorer housing with less control over temperature and noise fluctuations, below-average nutrition, and limited access to health care. Nonetheless, psychosocial factors may contribute to increased rates of illness in these individuals. Wright et al., (1998) argue, for example, that the recently acknowledged increase in asthma incidence may be related to life stress in addition to exposure to indoor allergens and outdoor air pollutants. Psychological stress may increase illness susceptibility in at least two ways. First, psychological stress may increase the likelihood of health-compromising behavior. Initiation of substance use, for example, has been linked to emotional distress of early-maturing girls or late-maturing boys (Tschann et al., 1994). Alcohol abuse and alcohol-related mortality are both most prevalent among lower SES individuals (Makela, 1999). Interestingly, alcohol markedly increased the lead-induced neurochemical and neurobehavioral toxicity in 3-month-old Wistar rats (Gupta and Gill, 2000). Physical overexertion and loss of sleep also has been reported to impair health in rats (Toth, 1995; Everson and Toth, 2000) and humans (Konig et al., 2000), which may be associated secondarily with psychological stress. Psychological stress also may exert an influence on the same biological processes that are affected by toxicant exposure, thereby magnifying toxicity. At present, data for this second possibility are generally lacking. The aim of this mini-review is to discuss the effects of stress on the immune system and on some of the biological pathways that mediate this influence. We believe, especially in light of the controversial nature and unknown etiological mechanisms of chronic fatigue...
syndrome, sick building syndrome, and multiple chemical sensitivity, that toxicological investigations might benefit from consideration of known psychoneuroimmunological mechanisms.

Psychological stress, like chemical and physical stressors, can exert an effect on immune reactivity and on disease, although it is important to make a distinction between transient stress and stress that exists over longer periods (as in the case of low SES-associated factors, for example). Moreover, although popular conception has it that stress impairs the immune system, some studies have suggested that acute stress actually might facilitate some aspects of immune function. For example, rats subjected to restraint exhibit more robust antigen-specific delayed-type hypersensitivity (DTH) responses than do control animals, when the stress is applied either on initial antigen exposure or on reexposure (Dhabhar, 1998). Human subjects exposed to a laboratory stressor (videotaped speech) (Larson et al., 2001) or engaging in tandem parachute jumping (Schedlowski et al., 1993) exhibit transient increases in natural killer-cell (NK) numbers and function. More intense and/or long-lived stressors, on the other hand, typically impair the same measures of immune function. Rats exposed to several weeks of daily restraint, for example, displayed marked declines in delayed-type hypersensitivity (DTH) responses (Dhabhar, 2000), and human subjects with histories of prolonged life stress exhibited reduced NK activity during and after a laboratory speech stress paradigm (Pike et al., 1997). A recent study showed that expression of the nuclear transcription factors AP-1 and NFκB in peripheral blood lymphocytes is markedly decreased in women experiencing distress associated with breast biopsy (Nagabhushan et al., 2001), suggesting a potential molecular mechanism for the immunosuppressive effects of profound stress.

Importantly, the impact of stress on immune function has been linked to increased vulnerability to illness. The stress associated with medical school exams (Glaser et al., 1987) or with caring for an individual with Alzheimer’s disease (Glaser and Kiecolt-Glaser, 1997; Cacioppo et al., 1998) impairs antiviral immunity and results in reactivation of latent viral infection and impaired responses to vaccination (Glaser et al., 1991, 1998, 2000; Kiecolt-Glaser et al., 1996). Psychological stress has also been shown to slow the process of wound healing (Kiecolt-Glaser et al., 1998; Marucha et al., 1998). Nonhuman primates undergoing maternal separation stress have shown marked and lasting changes in immune functions (Lubach et al., 1995; Coe, 1993) as well as increased vulnerability to parasitic infection (Bailey and Coe, 1999). In patients already diagnosed with disease, psychological stress is associated with poorer disease outcome. A recent prospective study in HIV-infected men found that severe stress, especially in combination with depression, predicted significant declines in CD4+ and CD8+ T lymphocyte numbers over the course of two years (Leserman et al., 1997). Analogous studies of simian immunodeficiency virus infection in nonhuman primates have shown that psychological stress is associated with shortened survival time (Capitanio and Lerce, 1998). In rats, emotional stressors that suppress NK function can render animals more susceptible to tumor colonization (Ben-Eliyahu et al., 1991). Importantly, cognitive behavioral interventions designed to alleviate the distress associated with HIV infection were effective in improving the immunological indices of disease course (Antoni et al., 1991, 2000; Cruess et al., 2000; Lutgendorf et al., 1997). There is similar evidence from studies of breast cancer patients that alleviation of psychological distress extends life expectancy (Spiegel et al., 1989), an effect thought to be mediated by having good quality social support (Turner-Cobb et al., 2000).

Underlying much of the literature on the immunomodulatory effects of stress is the assumption that stress affects each individual similarly. While there is ample evidence to support this assumption, there is nevertheless growing interest in the psychological and genetic variables that render some individuals particularly vulnerable. Changes in immune function during laboratory stressors, for example, are most profound in individuals with the greatest physiological reactivity to the stressor (Herbert et al., 1994), and there is reason to believe, from research on human subjects and nonhuman primates, that these differences in reactivity may be present very early in life (Kagan and Saudino, 2001; Suomi, 1999). The stress of beginning a new academic program impaired NK activity, particularly in students less optimistic about their likelihood of academic success (Segerstrom et al., 1998). Less sociable SIV-infected monkeys showed greater indications of early disease progression than did more sociable animals (Capitano et al., 1999). In short, psychological vulnerability to stress increases the immunological impact of the stressor.

Research into the mechanisms by which psychological stresses are translated into impaired immune function and vulnerability to disease has focused primarily on two pathways: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic branch of the autonomic nervous system (Fig. 1). Early work showed that adrenal glucocorticoids, the end products of HPA activation, influence multiple indices of immune reactivity (Adler et al., 1991), and it has been argued that glucocorticoid production is an important means by which the immune response can be contained (Munck et al., 1984). The discoveries that increases in glucocorticoids also occur during an immune response (Besedovsky et al., 1985), and that HPA activation can be induced by proinflammatory cytokines at the hypothalamic level (Sapolsky et al., 1985) suggest that the immune system makes use of the neuroendocrine system to rein itself in. Recent work, however, has suggested a more complex picture. Whereas acute exposure to high levels of glucocorticoids or prolonged exposure to moderate levels impair various aspects of immune function in vivo (Fleschner et al., 1996; Dhabhar and McEwen, 1999; Sheridan et al., 1998), there is now evidence that endogenous release of adrenal hormones may play a critical role in optimizing immune function. For example, adrenalectomized rats fail to mount a robust
antibody response to keyhole limpet hemacyanin (KLH) (Fleshner et al., 2001, Friedman and Irwin, 2001). Moreover, the antibody response to KLH is restored more effectively with properly timed corticosterone injections than with simple corticosterone replacement in the drinking water (Fleshner et al., 2001), suggesting a complex and finely tuned relationship between the immune and neuroendocrine systems. The suppression of mouse host resistance to \textit{L. monocytogenes} by cold-restraint stress has been shown to be mediated mainly by norepinephrine and lessened by corticosterone (Cao and Lawrence, work in progress). The involvement of glucocorticoids in stress-induced enhancement of DTH responses, mediated largely through influence on the trafficking of cells to the skin compartment (Dhabhar and McEwen, 1999) further undermines the view that HPA activation suppresses immune function. Nonetheless, the existence of glucocorticoid receptors on the surfaces of multiple populations of immunocompetent cells (Cupps and Fauci, 1982), as well as evidence for the production of glucocorticoids in primary lymphoid tissue (Ashwell et al., 2000), provides the means by which aberrant levels of adrenal hormones associated with chronic stress or vulnerability to stress might exert a negative influence on immune function. Even neuropeptides usually thought to be confined to the brain, such as hypothalamic corticotropin-releasing hormone, have been shown to peripherally influence immune reactivity (Baigent, 2001; McEvoy et al., 2001).

The sympathetic nervous system (SNS) is the second major route by which psychological experience can influence immune reactivity. It has been known since the mid-1980s that SNS cells make synapse-like contacts with lymphocytes in primary and secondary lymphoid tissue (Felten et al., 1987), and that the local release or exogenous administration of sympathetic hormones, such as norepinephrine and neuropeptide \( Y \), can influence the reactivity of immunocompetent cells (Friedman et al., 1995; Madden et al., 1995). Many immunocompetent cells bear adrenergic receptors, although the distribution of specific types of these receptors is not uniform and creates the opportunity for fine-tuned regulation of the immune response. For example, Th1 and B cells, but not Th2 cells, express \( \beta_2 \)-adrenergic receptors, activation of which is typically associated with increased intracellular cAMP and inhibition of cell function (Sanders et al., 1997). As for adrenal hormones, there is evidence that sympathetic activation is involved in the immunomodulatory effects of stress (Friedman and Irwin, 1995). For example, stress reduces NK activity and increases tumor colonization in rats through activation of \( \beta_2 \)-adrenergic receptors (Shakhar et al., 1998). Moreover, altered sympathetic function is implicated in impaired immune function associated with clinical depression (Irwin, 1995). Temporary ablation of SNS fibers with the selective denervation of peripheral noradrenergic nerves by 6-hydroxydopamine (6-OHDA) enhanced early host resistance to \textit{Listeria monocytogenes} (Rice et al., 2001), suggesting that norepinephrine inhibits host resistance. However, there is also evidence that local release of norepinephrine facilitates some immune functions. Destruction of peripheral sympathetic neurons, for example, results in markedly reduced production of antigen-specific antibodies, suggesting that sympathetic activation of antigen-specific \( \beta_2 \)-adrenergic receptor-positive B cells is critical for an optimal humoral immune response (Kohm and Sanders, 1999). The recent observation that norepinephrine release from the spleen and bone marrow increases during \textit{in vivo} activation of antigen-specific Th2 and B cells (Kohn et al., 2000) underscores the potential role for the SNS in optimal immune function.

Although the literature on immunomodulation by endocrine, neuroendocrine, and autonomic systems is large, far less is known about how the brain regulates immune function. What is known implicates the same areas of the brain that are
sensitive to psychological stress. For example, we recently showed that administration of 6-OHDA, an agent that selectively depletes catecholaminergic neurons, into the striatum of the mouse, compromised host resistance to *L. monocytogenes* as well as the primary antibody response and the DTH response to KLH (Filipov *et al.*, 2001a,b). Of potential importance, partial (40%) sparing of striatal dopamine by coadministration of an uptake inhibitor along with the 6-OHDA, restored host resistance to *L. monocytogenes* but did not restore the antibody or DTH response. This result suggests that striatal dopamine systems differentially regulate innate and acquired immune responses. Other studies of brain regulation of immune function have implicated other specific regions, such as the locus coeruleus (Rassnick *et al.*, 1994) and the limbic system (Jurkowski *et al.*, 2001), as well as specific neurochemical systems such as dopamine, serotonin, and GABA (Devoino *et al.*, 1994), all of which are known to be involved in the brain’s response to psychological stressors. Interestingly, it has been suggested that psychological stress alone can induce the expression of cytokines in the brain (Nguyen *et al.*, 1998), and stress-induced activation of the HPA axis may be mediated by cytokine release in the brain (Saperstein *et al.*, 1992).

As a final intriguing note, there is compelling evidence that regulation of immune function by the brain is asymmetrical. For example, greater electroencephalographic activation of the right frontal region of the brain, relative to the left, was associated with reduced NK activity in twenty healthy women (Kang *et al.*, 1991). In animals, brain laterality effects on peripheral immune reactivities have previously been demonstrated based on paw preference (Neveu, 1993), and after lesioning right versus left cortical ((Neveu, 1988, Neveu *et al.*, 1991) or subcortical areas (Neveu *et al.*, 1992). The complexities associated with psychoneuroimmunological interactions are further exemplified by evidence demonstrating that genetically identical (inbred) BALB/c mice are behaviorally different (preferential left versus right turning), and their behavioral asymmetry influences their immune responsiveness. Right-turning (left-brain dominant) mice had greater primary antibody responses and DTH to KLH and better host resistance to *L. monocytogenes* than left-turning (right-brain dominant) mice (Kim *et al.*, 1999). It is important to note that brain laterality differences have also been correlated with differential sensitivity to stress (Westergaard *et al.*, 2001). Stress can induce a lateralized generation of neurotransmitter metabolites (Carlson *et al.*, 1991), which is dependent on the type and duration of the stress (Carlson *et al.*, 1991; Neveu and Moya, 1997; Sullivan and Gratton, 1998). Although cortical dopamine and plasma corticosterone levels (HPA axis) of rats were positively associated after mild physical (2-min tail pinch) and psychological (15-min exposure to cat odors) stress, this relationship was asymmetrical only for the psychological stress (Sullivan and Gratton, 1998). Even prenatal stress has been reported to affect later behavior in an asymmetrical fashion (Alonso *et al.*, 1997), and there is evidence that prenatal stress can modify immune reactivity in neonates (Coe *et al.*, 1999).

Asymmetric brain regulation of immune function may provide a scientific meeting point for psychoneuroimmunology and neurotoxicology. The environmental toxicant lead has been shown to differentially affect immunity of mice based on their brain laterality (Kim *et al.*, 2000), and lead exacerbates CNS control of sickness behavior (Dyatlov *et al.*, in press) including elevated levels of IL-1 and IL-6. Neveu *et al.* (1998) have reported that right-pawed mice were more sensitive to IL-1-induced sickness than were left-pawed animals. The combination of chemical, physical, and psychological stresses (Fig. 2) during early development may be especially critical, in that prenatal stress can mediate behavioral and immune changes later in life. These early stresses may influence the brain laterality itself since it is known that hemisphere dominance is not genetic. Mice can be bred for high or low preference, but not for right versus left dominance (Collins, 1991). The immunomodulatory effects of lead as well as other environmental agents, via central and peripheral means, emphasize the need to consider neuroendocrine immune interactions for evaluation of environmental stressors. Since some environmental pollutants such as lead are already classified as neurotoxicants and immunotoxicants, it is especially important to consider their modulation of neuroimmunological circuitry in conjunction with psychological stress. These combined stresses on early developmental patterns may substantially alter the threshold tolerance for later stresses and exacerbate the detrimental outcomes of such occurrences.

**REFERENCES**


