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Stress-induced Changes in Immune Cell Distribution and Trafficking: Implications for Immunoprotection versus Immunopathology

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1. Introduction

Effective immunoprotection requires rapid recruitment of leukocytes into sites of surgery, wounding, infection, or vaccination. Immune cells circulate continuously on surveillance pathways that take them from the blood, through various organs, and back into the blood. This circulation is essential for the maintenance of an effective immune defense network (Sprent and Tough, 1994). The numbers and proportions of leukocytes in the blood provide an important representation of the state of distribution of leukocytes in the body and of the state of activation of the immune system. A stress-induced change in leukocyte distribution within different body compartments is perhaps one of the most underappreciated effects of stress and stress hormones on the immune system.

Because the blood is the most accessible and commonly used compartment for human studies, it is important to carefully evaluate how changes in blood immune parameters might reflect *in vivo* immune function in the context of the specific experiments or study at hand. Moreover, because most blood collection procedures involve a certain amount of stress, because all patients or subjects will have experienced acute and chronic stress, and because many studies of psychophysiological effects on immune function focus on stress, it is important to keep in mind the effects of stress on blood leukocyte distribution.

Numerous studies have shown that stress and stress hormones induce significant changes in absolute numbers and relative proportions of leukocytes in the blood. In fact, changes in blood leukocyte numbers were used as an indirect measure for changes in plasma cortisol before methods were available to directly assay the hormone (Hoagland *et al.*, 1946), and numerous studies have shown that glucocorticoid hormones induce significant changes in blood leukocyte distribution (Fauci and Dale, 1974, 1975; Dhabhar *et al.*, 1996). Studies have also delineated the rapid and significant effects of catecholamine hormones in mediating stress-induced changes in

blood leukocyte distribution (Benschop *et al.*, 1993, 1996; Carlson *et al.*, 1997; Mills *et al.*, 1998, 2001; Redwine *et al.*, 2003).

Dhabhar *et al.* were the first to propose that stress-induced changes in blood leukocyte distribution may represent an adaptive response (Dhabhar *et al.*, 1994; Dhabhar and McEwen, 1999a). They suggested that acute stress–induced changes in blood leukocyte numbers represent a redistribution of leukocytes from the blood to other organs such as the skin and lining of the gastrointestinal and urinary-genital tracts and draining sentinel lymph nodes (Dhabhar and McEwen, 1996a, 2001). They hypothesized that such a leukocyte redistribution may enhance immune function in those compartments to which immune cells traffic during stress. In agreement with this hypothesis, it was demonstrated that a stress-induced redistribution of leukocytes from the blood to the skin is accompanied by a significant enhancement of skin immunity (Dhabhar and McEwen, 1996, 1999a; Dhabhar *et al.*, 2000). Studies also showed that acute stress initially increases trafficking of all leukocyte subpopulations to a site of surgery or immune activation (Viswanathan and Dhabhar, 2005). Although all leukocyte subpopulations traffic to a site of immune activation in greater numbers during stress, tissue damage, antigen-, or pathogen-driven chemoattractants synergize with acute stress to determine which specific subpopulations are recruited more vigorously (Viswanathan and Dhabhar, 2005). Thus, depending on the primary chemoattractants driving an immune response, acute stress may selectively mobilize specific leukocyte subpopulations into sites of surgery, wounding, or immune activation. Such a stress-induced increase in leukocyte trafficking may be an important mechanism by which acute stressors alter the course of different (innate versus adaptive, early versus late, or acute versus chronic) immune responses.

It is important to keep in mind the Yin-Yang nature of a stress-induced increase in leukocyte trafficking to sites of immune activation. Such an increase in leukocyte trafficking may be beneficial for promoting immunoprotection during surgery, wound healing, vaccination, infection, or localized cancer. However, a stress-induced increase in leukocyte trafficking may have harmful consequences during stress-induced exacerbations of inflammatory (e.g., cardiovascular disease, gingivitis) and autoimmune (e.g., psoriasis, arthritis, multiple sclerosis) diseases (Amkraut *et al.*, 1971; Al'Abadie *et al.*, 1994; Garg *et al.*, 2001; Ackerman *et al.*, 2002) or graft-rejection (Kok-van Alphen and Volker-Dieben, 1983). Whereas decades of research have examined the pathological effects of stress on immune function and on health, the study of salubrious or health-promoting effects of stress is relatively new (Dhabhar *et al.*, 1995a; Dhabhar and McEwen, 2001). Much work remains to be done to elucidate the mechanisms mediating these bidirectional effects of stress on health and to translate basic findings regarding the adaptive effects of stress from bench to bedside. Here we discuss stress-induced and stress hormone–induced changes in blood leukocyte distribution and examine their functional consequences.

2. Stress

Although the word *stress* generally has negative connotations, stress is a familiar aspect of life, being a stimulant for some but a burden for others. Numerous definitions have been proposed for the word *stress*. Each definition focuses on aspects of an internal or external challenge, disturbance, or stimulus; on perception of a stimulus by an organism; or on a physiological response of the organism to the stimulus (Goldstein and McEwen, 2002; McEwen, 2002; Sapolsky, 2004). Physical stressors have been defined as external challenges to homeostasis and psychological stressors as the "anticipation justified or not, that a challenge to homeostasis looms" (Sapolsky, 2005). An integrated definition states that stress is a constellation of events, consisting of a stimulus (stressor), which precipitates a reaction in the brain (stress perception), which activates physiologic fight-or-flight systems in the body (stress response) (Dhabhar and McEwen, 1997). The physiologic stress response results in the release of neurotransmitters and hormones that serve as the brain's alarm signals to the rest of the body. It is often overlooked that a stress response has salubrious adaptive effects in the short run (Dhabhar *et al.*, 1995a; Dhabhar and McEwen, 1996, 2001) although stress can be harmful when it is longlasting (Irwin *et al.*, 1990; McEwen, 1998; Sapolsky, 2004). An important distinguishing characteristic of stress is its duration and intensity. Thus, *acute stress* has been defined as stress that lasts for a period of a few minutes to a few hours and *chronic stress* as stress that persists for several hours per day for weeks or months (Dhabhar and McEwen, 1997). The intensity of stress may be gauged by the peak levels of stress hormones, neurotransmitters, and other physiological changes such as increases in heart rate and blood pressure, and by the amount of time for which these changes persist during and after the cessation of stress.

It is important to bear in mind that there exist significant individual differences in the manner and extent to which stress is perceived, processed, and coped with. These differences become particularly relevant in case of human subjects because stress perception, processing, and coping mechanisms can have significant effects on the kinetics and peak levels of circulating stress hormones and on the duration for which these hormone levels are elevated. The magnitude and duration of catecholamine and glucocorticoid hormone exposure in turn can have significant effects on leukocyte distribution and function (Dhabhar and McEwen, 2001; Pruett, 2001; Schwab *et al.*, 2005).

3. Stress-induced Changes in Blood Leukocyte Numbers

The phenomenon of acute stress–induced changes in blood leukocyte numbers is well-known. Changes in blood leukocyte numbers were used as an indirect measure for changes in plasma cortisol levels long before

methods were available to directly assay the hormone (Hoagland *et al.*, 1946). Stress-induced changes in blood leukocyte numbers have been reported in fish (Pickford *et al.*, 1971), hamsters (Bilbo *et al.*, 2002), mice (Jensen, 1969), rats (Dhabhar *et al.*, 1994, 1995a, 1996; Rinder *et al.*, 1997), rabbits (Toft *et al.*, 1993), horses (Snow *et al.*, 1983), non-human primates (Morrow-Tesch *et al.*, 1993), and humans (Herbert and Cohen, 1993; Schedlowski *et al.*, 1993a; Mills *et al.*, 1998; Bosch *et al.*, 2003; Redwine *et al.*, 2004). This suggests that the phenomenon of stress-induced leukocyte redistribution has a long evolutionary lineage and that perhaps it has important functional significance.

Studies in rodents have shown that stress-induced changes in blood leukocyte numbers are characterized by a significant decrease in numbers and percentages of lymphocytes and monocytes and by an increase in numbers and percentages of neutrophils (Dhabhar *et al.*, 1994, 1995a). Flow cytometric analyses have revealed that absolute numbers of peripheral blood T cells, B cells, NK cells, and monocytes all show a rapid and significant decrease (40% to 70% lower than baseline) during stress (Dhabhar *et al.*, 1995a). Moreover, it has been shown that stress-induced changes in leukocyte numbers are rapidly reversed upon the cessation of stress (Dhabhar *et al.*, 1995a). In apparent contrast with animal studies, human studies have shown that stress can increase rather than decrease blood leukocyte numbers (Naliboff *et al.*, 1991; Schedlowski *et al.*, 1993a; Brossschot *et al.*, 1994; Mills *et al.*, 1995; Bosch *et al.*, 2003). Factors that help resolve this apparent contradiction are discussed later in this chapter.

4. Hormones Mediating Stress-induced Changes in Blood Leukocyte Numbers

The catecholamines epinephrine and norepinephrine and the glucocorticoid hormones have been identified as the major endocrine mediators of stress-induced changes in leukocyte distribution (Fauci and Dale, 1974; Schedlowski *et al.*, 1993a, 1993b; Dhabhar *et al.*, 1995a; Benschop *et al.*, 1996; Dhabhar *et al.*, 1996). Studies have revealed that stress-induced changes in leukocyte distribution are mediated by hormones released by the adrenal gland (Dhabhar *et al.*, 1996; Dhabhar and McEwen, 1999b). Adrenalectomy (which eliminates the corticosterone and epinephrine stress response) has been shown to reduce the magnitude of the stress-induced changes in blood leukocyte numbers. (Dhabhar *et al.*, 1996; Dhabhar and McEwen, 1999b). Cyanoketone treatment, which virtually eliminates the corticosterone stress response, also virtually eliminates the stress-induced decrease in blood lymphocyte numbers, and significantly enhances the stress-induced increase in blood neutrophil numbers (Dhabhar *et al.*, 1996). Several other studies have shown that glucocorticoid treatment induces changes in leukocyte distribution in mice (Dougherty and White, 1945; Spain and Thalhimer, 1951;

Cohen, 1972; Zatz, 1975), guinea pigs (Fauci, 1975), rats (Ulich *et al.*, 1988; Miller *et al.*, 1994; Dhabhar *et al.*, 1996), rabbits (Miller *et al.*, 1994), and humans (Fauci and Dale, 1974; Fauci, 1976; Onsrud and Thorsby, 1981).

Because adrenal steroids act at two distinct receptor subtypes that show a heterogeneity of expression in immune cells and tissues (Spencer *et al.*, 1990, 1991; Miller *et al.*, 1990, 1991, 1992, 1993; Dhabhar *et al.*, 1993, 1995b, 1996), Dhabhar *et al.* investigated the role played by each receptor subtype in mediating changes in leukocyte distribution (Dhabhar *et al.*, 1996). Acute administration of aldosterone (a specific type I adrenal steroid receptor agonist) to adrenalectomized animals did not have a significant effect on blood leukocyte numbers. In contrast, acute administration of corticosterone (the endogenous type I and type II receptor agonist) or RU28362 (a specific type II receptor agonist) to adrenalectomized animals induced changes in leukocyte distribution that were similar to those observed in intact animals during stress. These results suggest that corticosterone, acting at the type II adrenal steroid receptor, is a major mediator of the stress-induced decreases in blood lymphocyte and monocyte distribution. Taken together, these studies show that stress and glucocorticoid hormones induce a significant decrease in blood lymphocyte numbers when administered under acute or chronic conditions.

Apart from glucocorticoids, studies have also demonstrated the importance of catecholamine hormones in mediating stress-induced changes in blood leukocyte distribution in rodents and humans (Benshop *et al.*, 1993, 1996; Schedlowski *et al.*, 1993b; Carlson *et al.*, 1997; Mills *et al.*, 1998; Mills *et al.*, 2001; Redwine *et al.*, 2003; Engler *et al.*, 2004). In apparent contrast with glucocorticoid hormones, catecholamine hormones have been shown to increase blood leukocyte numbers in rats (Harris *et al.*, 1995) and humans (Landmann *et al.*, 1984). On closer examination, it is observed that after adrenaline or noradrenaline administration, neutrophil and NK cell numbers increase rapidly and dramatically whereas T- and B-cell numbers decrease (Tonnesen *et al.*, 1987; Landmann, 1992; Schedlowski *et al.*, 1993b; Benschop *et al.*, 1996). Carslon *et al.* have shown that catecholamine pretreatment results in increased accumulation of lymphocytes in the spleen and lymph nodes (Carlson *et al.*, 1997), which would be in agreement with a catecholamine-induced decrease in lymphocytes in the blood. By acutely administering epinephrine, norepinephrine, selective α and β adrenergic receptor agonists, or corticosterone to adrenalectomized animals, researchers have shown that increases in blood granulocyte numbers may be mediated by the α_1 and β adrenergic receptors and are counteracted by corticosterone acting at the type II adrenal steroid receptor (Dhabhar and McEwen, 1999b). Increases in lymphocytes may be mediated by the α_2 receptor, whereas decreases in lymphocytes may be mediated by β adrenergic and type II adrenal steroid receptors (Dhabhar and McEwen, 1999b).

Therefore, the absolute number of specific blood leukocyte subpopulations may be significantly affected by the ambient concentrations of epi-

nephrine, norepinephrine, and corticosterone. Differences in concentrations and combinations of these hormones may explain reported differences in blood leukocyte numbers during different stress conditions (e.g., short-versus long-duration acute stress, acute versus chronic stress) and during exercise.

5. A Stress-induced Decrease in Blood Leukocyte Numbers Represents a Redistribution Rather Than a Destruction or Net Loss of Blood Leukocytes

From the above discussion it is clear that stress and glucocorticoid hormones induce a rapid and significant decrease in blood lymphocyte, monocyte, and NK cell numbers. This decrease in blood leukocyte numbers may be interpreted in two possible ways. It could reflect a large-scale destruction of circulating leukocytes. Alternatively, it could reflect a redistribution of leukocytes from the blood to other organs in the body. In favor of the latter explanation, experiments were conducted to test the hypothesis that acute stress induces a redistribution of leukocytes from the blood to other compartments in the body (Dhabhar *et al.*, 1995a).

The first series of experiments examined the kinetics of recovery of the stress-induced reduction in blood leukocyte numbers. It was hypothesized that if the observed effects of stress represented a redistribution rather than a destruction of leukocytes, one would see a relatively rapid return of leukocyte numbers back to baseline upon the cessation of stress. Results showed that all leukocyte subpopulations that showed a decrease in absolute numbers during stress showed a complete recovery with numbers reaching pre-stress baseline levels within 3 h after the cessation of stress (Dhabhar *et al.*, 1995a). Plasma levels of lactate dehydrogenase (LDH), which is a marker for cell damage, were also monitored in the same experiment. If the stress-induced decrease in leukocyte numbers were the result of a destruction of leukocytes, one would expect to observe an increase in plasma levels of LDH during or after stress. However, no significant changes in plasma LDH were observed, further suggesting that a redistribution rather than a destruction of leukocytes was primarily responsible for the stress-induced decrease in blood leukocyte numbers (Dhabhar *et al.*, 1995a). Further studies have shown that lymph nodes, bone marrow, and skin are target organs of a stress-induced redistribution of leukocytes within the body (Dhabhar, 1998; Stefanski, 2003; Viswanathan and Dhabhar, 2005).

It is important to bear in mind that although glucocorticoids are known to induce leukocyte apoptosis under certain conditions (Cohen, 1992), glucocorticoid hormones have also been shown to induce changes in various immune parameters (Munck *et al.*, 1984), including immune cell distribution (Dhabhar *et al.*, 1995a; Dhabhar and McEwen, 2001), in the absence of

cell death. It has been suggested that some species may be "steroid-resistant" and others may be "steroid-sensitive," and that glucocorticoid-induced changes in blood leukocyte numbers represent changes in leukocyte redistribution in steroid-resistant species (humans and guinea pig), and leukocyte lysis in steroid-sensitive species (mouse and rat) (Claman, 1972). However, it is now accepted that even in species previously thought to be steroid-sensitive, changes in adrenal steroids similar to those described here produce changes in leukocyte distribution rather than an increase in leukocyte destruction (Cohen, 1972).

6. Target Organs of a Stress-induced Redistribution of Blood Leukocytes

Based on the above discussion, the obvious question one might ask is, "Where do blood leukocytes go during stress?" Numerous studies using stress or stress hormone treatments have investigated this issue. Using gamma imaging to follow the distribution of adoptively transferred radio-labeled leukocytes in whole animals, Toft *et al.* have shown that stress induces a redistribution of leukocytes from the blood to the mesenteric lymph nodes (Toft *et al.*, 1993). It has been reported that anesthesia stress, as well as the infusion of ACTH and prednisolone in rats results in decreased numbers of labeled lymphocytes in the thoracic duct, and the cessation of drug infusion results in normal circulation of labeled lymphocytes (Spry, 1972). This suggests that ACTH and prednisolone (which would produce hormonal changes similar to those observed during stress) may cause the retention of circulating lymphocytes in different body compartments thus resulting in a decrease in lymphocyte numbers in the thoracic duct and a concomitant decrease in numbers in the peripheral blood (Spry, 1972). It has also been reported that a single injection of hydrocortisone, prednisolone, or ACTH results in increased numbers of lymphocytes in the bone marrow of mice (Cohen, 1972), guinea pigs (Fauci, 1975), and rats (Cox and Ford, 1982). Fauci *et al.* have suggested that glucocorticoid-induced decreases in blood leukocyte numbers in humans may also reflect a redistribution of immune cells to other organs in the body (Fauci and Dale, 1974). Finally, corticosteroids have been shown to induce the accumulation of lymphocytes in mucosal sites (Walzer *et al.*, 1984), and the skin has been identified as a target organ to which leukocytes traffic during stress (Dhabhar and McEwen, 1996; Viswanathan and Dhabhar, 2005). *In vitro* catecholamine treatment has also been shown to direct leukocyte traffic to spleen and lymph nodes (Carlson *et al.*, 1997). Studies have identified lymph nodes, bone marrow, and skin as the target organs of a stress-induced redistribution of leukocytes within the body (Dhabhar, 1998; Stefanski, 2003; Viswanathan and Dhabhar, 2005).

It is important to note that in these studies, a return to basal glucocorticoid levels was followed by a return to basal blood lymphocyte numbers, further supporting the hypothesis that decrease in blood leukocyte numbers is the result of a glucocorticoid-induced redistribution rather than a glucocorticoid-induced destruction of blood leukocytes. The above discussion shows that a stress-induced decrease in blood leukocyte numbers reflects a redistribution or redeployment of leukocytes from the blood to other organs (lymph nodes, bone marrow, and skin) in the body.

7. Acute Stress-induced Changes in Blood Leukocyte Numbers: Contradicting Results or a Biphasic Response?

As stated before, stress has been shown to induce a significant decrease in blood leukocyte numbers in a range of different species. However, studies have also shown that stress can increase rather than decrease blood leukocyte numbers in humans (Naliboff *et al.*, 1991; Schedlowski *et al.*, 1993a; Brosschot *et al.*, 1994; Mills *et al.*, 1995; Bosch *et al.*, 2003). This apparent contradiction is resolved when three important factors are taken into account: first, stress-induced increases in blood leukocyte numbers are observed after stress conditions that primarily result in the activation of the sympathetic nervous system. These stressors are often of a short duration (few minutes) or relatively mild (e.g., public speaking) (Naliboff *et al.*, 1991; Schedlowski *et al.*, 1993a; Brosschot *et al.*, 1994; Mills *et al.*, 1995). Second, the increase in leukocyte numbers may be accounted for by stress- or catecholamine-induced increases in granulocytes and NK cells (Naliboff *et al.*, 1991; Schedlowski *et al.*, 1993a; Brosschot *et al.*, 1994; Mills *et al.*, 1995; Benschop *et al.*, 1996). Because granulocytes form large proportion of circulating leukocytes in humans (60–80% granulocytes), an increase in granulocyte numbers is reflected as an increase in total leukocyte numbers in contrast with rats and mice (10–20% granulocytes). Third, stress or pharmacologically induced increases in glucocorticoid hormones induce a significant decrease in blood lymphocyte and monocyte numbers (Hoagland *et al.*, 1946; Stein *et al.*, 1951; Schedlowski *et al.*, 1993a; Dhabhar *et al.*, 1996). Thus, stress conditions that result in a significant and sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis will result in a decrease in blood leukocyte numbers.

In view of the above discussion, it may be proposed that acute stress induces an initial increase followed by a decrease in blood leukocyte numbers. Stress conditions that result in activation of the sympathetic nervous system, especially conditions that induce high levels of norepinephrine, may induce an increase in circulating leukocyte numbers. These conditions may occur during the very beginning of a stress response, very

short duration stress (order of minutes), mild psychological stress, or during exercise. In contrast, stress conditions that result in the activation of the HPA axis induce a decrease in circulating leukocyte numbers. These conditions often occur during the later stages of a stress response, long-duration acute stressors (order of hours), or during severe psychological, physical, or physiological stress. An elegant and interesting example in support of this hypothesis comes from Schedlowski *et al.* who measured changes in blood T cell and NK cell numbers as well as plasma cate-cholamine and cortisol levels in parachutists (Schedlowski *et al.*, 1993a). Measurements were made 2 h before, immediately after, and 1 h after the jump. Results showed a significant increase in T cell and NK cell numbers immediately (minutes) after the jump that was followed by a significant decrease 1 h after the jump. An early increase in plasma catecholamines preceded early increases in lymphocyte numbers, whereas the more delayed rise in plasma cortisol preceded the late decrease in lymphocyte numbers (Schedlowski *et al.*, 1993a). Importantly, changes in NK cell activity and antibody-dependent cell-mediated cytotoxicity closely paralleled changes in blood NK cell numbers, thus suggesting that changes in leukocyte numbers may be an important mediator of apparent changes in leukocyte "activity." Similarly, Rinner *et al.* have shown that a short stressor (1-min handling) induced an increase in mitogen-induced proliferation of T and B cells obtained from peripheral blood, whereas a longer stressor (2-h immo-bilization) induced a decrease in the same proliferative responses (Rinner *et al.*, 1992). In another example, Manuck *et al.* showed that acute psycho-logical stress induced a significant increase in blood Cytolytic T Lympho-cyte (CTL) numbers only in those subjects who showed heightened catecholamine and cardiovascular reactions to stress (Manuck *et al.*, 1991).

Thus, an acute stress response may induce biphasic changes in blood leukocyte numbers. Soon after the beginning of stress (order of minutes) or during mild acute stress or exercise, catecholamine hormones and neu-rotransmitters induce the body's "soldiers" (leukocytes) to exit their "barracks" (spleen, lung, marginated pool, and other organs) and enter the "boulevards" (blood vessels and lymphatics). This results in an increase in blood leukocyte numbers, the effect being most prominent for NK cells and granulocytes. As the stress response continues, activation of the HPA axis results in the release of glucocorticoid hormones that induce leukocytes to exit the blood and take position at potential "battle stations" (skin, mucosal lining of gastrointestinal and urinary-genital tracts, lung, liver, and lymph nodes) in preparation for immune challenges that may be imposed by the actions of the stressor (Dhabhar *et al.*, 1995a; Dhabhar and McEwen, 1996, 2001). Such a redistribution of leukocytes results in a decrease in blood leukocyte numbers, the effect being most prominent for T and B lympho-cytes, NK cells, and monocytes. Thus, acute stress may result in a redistrib-ution of leukocytes from the barracks, through the boulevards, and to potential battle stations within the body.

8. Stress-induced Redistribution of Blood Leukocytes: Molecular Mechanisms

It is likely that the observed changes in leukocyte distribution are mediated by changes in either the expression, or affinity, of adhesion molecules on leukocytes and/or endothelial cells. It has been suggested that after stress or after glucocorticoid treatment, specific leukocyte subpopulations (being transported by blood and lymph through different body compartments) may be selectively retained in those compartments in which they encounter a stress- or glucocorticoid-induced "adhesion match" (Dhabhar and McEwen, 1999a). As a result of this selective retention, the proportion of specific leukocyte subpopulations would decrease in the blood, whereas it increases in the organ in which they are retained (e.g., the skin) (Viswanathan and Dhabhar, 2005).

Support for this hypothesis comes from studies that show acute psychological stressors such as public speaking can induce significant changes in leukocyte adhesion molecules (Mills and Dimsdale, 1996; Goebel and Mills, 2000; Bauer *et al.*, 2001; Redwine *et al.*, 2003, 2004; Shephard, 2003). Prednisolone has also been shown to induce the retention of circulating lymphocytes within the bone marrow, spleen, and some lymph nodes thus resulting in a decrease in lymphocyte numbers in the thoracic duct and a concomitant decrease in numbers in the peripheral blood (Spry, 1972; Cox and Ford, 1982). Moreover, glucocorticoid hormones also influence the production of cytokines (Danes and Araneo, 1989) and lipocortins (Hirata, 1989), which in turn can affect the surface adhesion properties of leukocytes and endothelial cells. Further investigation of the effects of endogenous glucocorticoids (administered in physiologic doses and examined under physiologic kinetic conditions) on changes in expression/activity of cell surface adhesion molecules and on leukocyte–endothelial cell adhesion is necessary.

9. Stress-induced Redistribution of Blood Leukocytes: Functional Consequences

It has been proposed that a stress-induced decrease in blood leukocyte numbers may represent an adaptive response (Dhabhar *et al.*, 1994; Dhabhar and McEwen, 1999a, 2001) reflecting a redistribution of leukocytes from the blood to other organs such as the skin, lining of gastrointestinal and urinary-genital tracts, lung, liver, and lymph nodes, which may serve as potential "battle stations" should the body's defenses be breached. Furthermore, such a leukocyte redistribution may enhance immune function in those compartments to which leukocytes traffic during stress (Dhabhar *et al.*, 1994; Dhabhar and McEwen, 1996, 1999a).

Thus, an acute stress response may direct the body's "soldiers" (leukocytes), to exit their "barracks" (spleen and bone marrow), travel the "boulevards" (blood vessels), and take position at potential "battle stations" (skin, lining of gastrointestinal and urinary-genital tracts, lung, liver, and lymph nodes) in preparation for immune challenge (Dhabhar and McEwen, 1996, 1997, 1999a). In addition to sending leukocytes to potential "battle stations," stress hormones may also better equip them for "battle" by enhancing processes like antigen presentation, phagocytosis, and antibody production. Thus, a hormonal alarm signal released by the brain upon detecting a stressor may "prepare" the immune system for potential challenges (wounding or infection) that may arise due to the actions of the stress-inducing agent (e.g., a predator or attacker).

The above hypothesis has profound functional and therapeutic implications. Acute psycho-physiological stress may act as an endogenous adjuvant to bolster the effects of natural or therapeutic immunization. Indeed, studies have shown that acute stress administered at the time of primary (Dhabhar and Viswanathan, 2005; Viswanathan *et al.*, 2005) or secondary (Dhabhar and McEwen, 1996) immunization induces a significant increase in indices of innate (Baumann *et al.*, 1983; Pos *et al.*, 1988; Lyte *et al.*, 1990), cell-mediated (Dhabhar and McEwen, 1996, 1999a; Dhabhar *et al.*, 2000; Bilbo *et al.*, 2002; Saint-Mezard *et al.*, 2003), and humoral immunity (Zalcman *et al.*, 1991, 1993). Stress-induced trafficking of leukocytes to sites of immune activation or surgery may also enhance the rate of wound healing and recovery (Viswanathan and Dhabhar, 2005). It is important to keep in mind that a stress-induced increase in leukocyte trafficking to sites of immune activation is like a double-edged sword: it may be beneficial for promoting immunoprotection during surgery, wound healing, vaccination, infection, or localized cancer. However, it may also mediate stress-induced exacerbations of inflammatory (e.g., cardiovascular disease, gingivitis) and autoimmune (e.g., psoriasis, arthritis, multiple sclerosis) diseases (Amkraut *et al.*, 1971; Al Abadie *et al.*, 1994; Garg *et al.*, 2001; Ackerman *et al.*, 2002).

When interpreting data showing stress-induced changes in functional assays such as lymphocyte proliferation or NK activity, it may be important to bear in mind the effects of stress on the leukocyte composition of the compartment in which an immune parameter is being measured. For example, it has been shown that acute stress induces a redistribution of leukocytes from the blood to the skin and that this redistribution is accompanied by a significant enhancement of a skin cell mediated immune (CMI) response (Dhabhar and McEwen, 1996). In what might at first glance appear to be contradicting results, acute stress has been shown to suppress splenic and peripheral blood responses to T-cell mitogens (Cunnick *et al.*, 1990) and splenic IgM production (Zalcman and Anisman, 1993). However, it is important to note that in contrast with the skin that is enriched in leukocytes during acute stress, peripheral blood and spleen are relatively

depleted of leukocytes during acute stress. This stress-induced decrease in blood and spleen leukocyte numbers may contribute to the acute stress–induced suppression of immune function in these compartments.

Moreover, in contrast with acute stress, chronic stress has been shown to suppress skin CMI, and a chronic stress–induced suppression of blood leukocyte redistribution is thought to be one of the factors mediating the immunosuppressive effect of chronic stress (Dhabhar and McEwen, 1997). Again, in what might appear to be contradicting results, chronic stress has been shown to enhance mitogen-induced proliferation of splenocytes (Monjan and Collector, 1997) and splenic IgM production (Zalcman and Anisman, 1993). However, the spleen is relatively enriched in T cells during chronic glucocorticoid administration, suggesting that it may also be relatively enriched in T cells during chronic stress (Miller *et al.*, 1994), and this increase in spleen leukocyte numbers may contribute to the chronic stress–induced enhancement of immune parameters measured in the spleen.

It is also important to bear in mind that the heterogeneity of the stress-induced changes in leukocyte distribution (Dhabhar *et al.*, 1995a) suggests that using equal numbers of leukocytes in a functional assay may not account for stress-induced changes in relative percentages of different leukocyte subpopulations in the cell suspension being assayed. For example, samples that have been equalized for absolute numbers of total blood leukocytes from control versus stressed animals may still contain different numbers of specific leukocyte subpopulations (e.g., T cells, B cells, or NK cells). Such changes in leukocyte composition may mediate the effects of stress even in functional assays using equalized numbers of leukocytes from different treatment groups. This possibility needs to be taken into account before concluding that a given treatment changes an immune parameter on a "per cell" rather than a "per population" basis.

10. Conclusion

It is important to recognize that the relationship between the psychological and physiological manifestations of stress and immune function is complex. Whereas decades of research have examined the pathological effects of stress on immune function and on health, the study of salubrious or health-promoting effects of stress is relatively new (Dhabhar *et al.*, 1995a). Much work remains to be done to elucidate the mechanisms mediating these bidirectional effects of stress on health and to translate basic findings regarding the adaptive effects of stress from bench to bedside.

An important function of endocrine mediators released under conditions of acute stress may be to ensure that appropriate leukocytes are present in the right place and at the right time to respond to an immune challenge that might be initiated by the stress-inducing agent (e.g., attack by a preda-

tor, invasion by a pathogen, etc.). The modulation of immune cell distribution by acute stress may be an adaptive response designed to enhance immune surveillance and increase the capacity of the immune system to respond to challenge in immune compartments (such as the skin and the epithelia of lung, gastrointestinal and urinary-genital tracts) that serve as major defense barriers for the body. Thus, neurotransmitters and hormones released during stress may increase immune surveillance and help enhance immune preparedness for potential (or ongoing) immune challenge. Such stress-induced increases in leukocyte trafficking may enhance immunoprotection during surgery, vaccination, or infection but may also exacerbate immunopathology during inflammatory (cardiovascular disease, gingivitis) or autoimmune (psoriasis, arthritis, multiple sclerosis) diseases.

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