Recent advances in immunology, clarification and the psychophysiology of stress, continued progress in the discovery of emotional factors in relation to physical disease, and the finding of apparent immunological disturbances in conjunction with mental illness lead to this attempt at a theoretical integration of the relation of stress, emotions, and immunological dysfunction (especially autoimmunity), and disease, both physical and mental. At this stage, far more questions will be raised than answered. (Solomon & Moos 1964, p. 657).

Prologue

OVERVIEW

It has been over 33 years since the groundbreaking paper by Solomon and Moos (1964) on psychosocial influences on immune function was published. Despite much progress over the years, there are still many exciting but unanswered questions (Ader, Felten, & Cohen 1991; Cohen & Herbert 1996). This area of research was coined psychoneuroimmunology in the seminal paper by Solomon and Moos (1964) and was later termed psychoneuroimmunology (PNI) by Ader and Cohen (1981). Research in PNI focuses on bidirectional interactions among the central nervous system (CNS), endocrine system, and immune system (Solomon 1987). The major aim of this chapter is to provide a detailed overview of important physical, social, and inferential elements involved in PNI research, especially in regard to cellular immunity (see Chapter 16 of this volume for an overview of humoral immunity).

HISTORICAL BACKGROUND

The major source of morbidity and mortality for a large part of recorded history was due to infectious diseases. As reviewed by Silverstein (1989), long before the mechanisms of pestilence were discovered it was known that those who had survived an infectious disease were relatively safe from future infections from the same agent. Such observations were utilized by Edward Jenner, who developed one of the first effective vaccination procedures for smallpox. However, immunology as a science has its roots in the landmark experimental vaccination study of Louis Pasteur, who demonstrated in 1880 that specific immunity could be induced via modified pathogens that no longer posed a biological threat. Pasteur's experimental studies were able to explain in a more mechanistic fashion the earlier findings of Jenner.

Around the time of Pasteur's findings, one of the major historical debates in immunology was being staged and would continue for several decades. The debate centered on whether cellular (e.g., phagocyte) or humoral (e.g., antibody) immunity could best explain protection against infections. These aligned with the humoral camp dated back to Galen, who emphasized the importance of humors in health and disease. However, in 1884 Elie Metchnikoff advanced his theory of phagocytosis, which suggested the importance of cellular processes as a first line of defense against invading organisms. As is often the case with ideas that challenge existing paradigms, his theory met with fierce resistance, particularly from German researchers. Interestingly, Silverstein (1989) suggests that this debate may have also been fueled by the ongoing international politics between the major camps of humorists (Germany) and cellularists (France). Around 1888 it was found that serum free of cells had the ability to kill certain microorganisms. The following years witnessed emerging support for the importance of serum complement, which seemed more consistent with humoral perspectives of immunity. In addition, the research by von Behring and Kitasato
demonstrated the importance of antibody (Ab) in protection from diphtheria and tetanus and signaled the perceived decline of cellular mechanisms, with subsequent researchers focusing primarily on the humoral arm of the immune system for the next 50 years.

It was the emergence of several findings that were not readily interpretable solely in the context of humoral immunity that enabled the eventual acceptance of the importance of cellular mechanisms. For instance, the finding that graft rejection was mediated by genetics and the demonstration of immunologic tolerance were difficult to explain from the perspective of humoral immunity. The end result of this historic debate was the acceptance that both cellular and humoral arms of the immune system were important for protection against infectious diseases and at least certain forms of malignant disease.

It is within this tradition that the immune system had historically been conceptualized as relatively autonomous in its regulation, reflecting specific and nonspecific responses to antigen (Ag) that emphasized both cellular and humoral responses. It is only relatively recently that CNS influences on immune function have been recognized in basic immunology texts (e.g., Roitt, Brostoff, & Male 1993, secs. 9.5–9.6). However, there are many exemplars of early researchers who were foresighted in their conceptualization of the immune system. For instance, Ishigami (1919) reported case studies suggesting that anxiety on the part of tuberculosis patients was associated with a poorer prognosis owing to immune system changes. Ishigami conducted a series of studies showing that glucose and EPI inhibited phagocytosis and might therefore be important factors influencing a link between anxiety and immunity. Ishigami (1919) speculated that the higher tuberculosis mortality rates in Japan’s student population may be due, in part, to the increased stress and anxiety in such individuals.

Ishigami’s studies were not representative of most immunological research at the time. However, the last 20 years have seen a dramatic increase in conceptually similar research that emphasizes the bidirectional relationships among the CNS, endocrine, and immune systems (Ader et al. 1991; Solomon & Moos 1964). Before we examine such research, we provide a detailed overview of basic cellular immune processes.

Physical Context: The Immune System

INTRODUCTION

The immune system is critical for the body’s defense against viruses, bacteria, and other foreign invaders, as well as malignant diseases (for reviews see Abbas, Lichtman & Pober 1994; Roitt et al. 1993; Schindler 1991; Scientific American 1993). Most pathogens and some tumor cells express surface molecules (antigens) that are different from "self" and are capable of inducing an immune response. There are two main components of the immune system: innate or natural immunity and specific or acquired immunity. Innate immunity generally refers to immune responses that are immediately available to protect the host even prior to exposure to a pathogen. These responses are relatively nonspecific (Abbas et al. 1994). Examples are the phagocytic cells such as neutrophils. Natural killer (NK) cells are also cells that are ready to kill virus-infected cells even before the infection takes place. In comparison, specific immunity is generally characterized by Ag recognition and stimulation. The response is specific and results in amplification of T- and B-lymphocyte populations as well as the production of memory cells that can be more quickly activated upon subsequent exposure to the same pathogen (Abbas et al. 1994).

There are at least five defining features of the specific immune response (Abbas et al. 1994). First, immune responses are specific for distinct Ags or pathogens. Lymphocytes recognize specific surface epitopes on Ags via membrane receptors. Second, immune responses are amazingly diverse. For instance, the typical individual has a lymphocyte repertoire that can discriminate at least 10^9 antigenic epitopes. Third, following initial exposure to Ag, immune responses are characterized by memory in which subsequent exposure to Ag (secondary immune response) leads to a larger, more rapid and effective immune response. The secondary immune response is made possible via a subset of memory lymphocytes that survive for long periods of time (as long as decades) in the absence of the Ag. Fourth, most normal immune responses are self-limiting following elimination of Ag. Finally, the immune response is remarkable in its ability to discriminate self from nonself. As a result, the immune system is typically able to recognize and mount an immune response to diverse Ags but not self Ags. Such immunological unresponsiveness is known as tolerance. Classically, specific immune responses can be characterized as cell-mediated or humoral. In this chapter we will focus on cell-mediated immunity but emphasize that, although separable, these are not independent aspects of the immune system.

The primary lymphoid organs are the thymus, bone marrow, and fetal liver. All hematopoietic cells appear to originate from bone marrow and fetal liver. The thymus is the site of T-cell maturation and it is there that self-tolerance is "learned." Immature T-cells are both CD4+ and CD8+. The CD8, or cluster of differentiation, refers to surface molecules that are associated with a particular cell lineage or stage of maturation and allows for the quantification of distinct lymphocyte populations. For instance, the CD4+ molecule is associated with helper T-cells, whereas the CD8+ molecule is associated with suppressor/cytotoxic T-cells. In the thymus, a process of positive selection occurs when immature T-cells bind with
either CD4+ or CD8+ molecules. T-cells that do not bind are eliminated. In addition, a process of negative selection occurs as T-cells that react to self molecules are eliminated.

The secondary lymphoid organs are the spleen, lymph nodes, and mucosa-associated lymphoid tissue (e.g., Peyer’s patches). Both primary and secondary lymphoid organs act as filters for the lymphatic system, which provides a microenvironment for Ag–immune cell interactions. The spleen provides an important site for immune responses to Ag in blood, whereas the lymph nodes provide an important site for immune responses to Ag in lymph.

The major cell populations of the cell-mediated immune response consist of helper T-cells, cytotoxic T-cells, suppressor T-cells, and NK cells. Helper T-cells serve to coordinate the different immune effector responses, whereas suppressor T-cells appear to turn off or down-regulate the immune response. Activation of helper T-cells occurs via their interactions with antigen presenting cells (APCs); these include cells such as macrophages and dendritic cells (e.g., Langerhans cells) that process the Ag and present it to helper T-cells in the context of major histocompatibility complex (MHC) class-II molecules. Briefly, MHC molecules (i.e., class-I and class-II) are membrane-associated gene products of the MHC. The MHC is a genetic region in all mammals whose normal biological function is signaling between lymphocytes and cells with MHC molecules. The MHC class-II molecules are distributed on cells involved in the immune response (e.g., APCs). These class-II molecules are synthesized in the endoplasmic reticulum, bind to peptides, and migrate to the cell surface. These peptides may then be displayed by APCs for recognition by helper T-cells, which in turn coordinate the different effector responses. See Table 1.

Helper T-cells have been classified into two types: Th1 and Th2 (Mosmann & Coffman, 1989). These helper T-cells secrete different cytokines that help to coordinate different effector responses. Cytokines are glycoprotein hormones produced by cells of the immune system (and other cells as well) and serve to regulate diverse aspects of immunity (Dinarello & Mier, 1987). For instance, Th1 helper T-cells produce interleukin-2 (IL-2), an important T-cell growth factor. Th1 cells also secrete interferon-gamma (IFN-γ), which leads to macrophage and NK cell activation; IFN-γ also has antiviral properties. In contrast, Th2 cells secrete IL-4, IL-5, and IL-10, which modulate B-cell class switching and Ab production. Once activated, each Th subset tends to inhibit expression of the other effector responses; for example, IL-10 inhibits IFN-γ production, whereas IFN-γ inhibits the production of Th2 cytokines.

Cytotoxic T-cells have the ability to lyse virus-infected and some malignant cells and to recognize specific Ags in the context of MHC class-I molecules, which are distributed on all nucleated cells and are synthesized in the cytosol of cells. The class-I molecules bind to peptides that have been degraded inside the cell and then migrate to the cell surface. In healthy cells these peptides are self-proteins. However, a virus-infected cell and some tumor cells will display foreign peptides that allow cytotoxic T-cells to destroy the cell.

Natural killer cells are large, granular lymphocytes that are capable of non-specifically lysing tumor and virus-infected cells. How NK cells recognize particular surface structures associated with infected cells is not understood. NK cells are abundant in the spleen and found in both blood and lymphoid tissue. They are responsive to cytokines – for example, IL-2, tumor necrosis factor (TNF-α), and IFN-γ – that serve to enhance their cytolytic

### Table 1: Description of Major Cells Associated with the Cellular Immune Response

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Surface Marker</th>
<th>Origin</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helper T-cells</td>
<td>CD4+</td>
<td>Thymus</td>
<td>Proliferation upon contact with Ag (MHC class-II restricted); coordinates different effector mechanisms of immune response via release of cytokines (e.g., IL-2)</td>
</tr>
<tr>
<td>Suppressor T-cells</td>
<td>CD8+</td>
<td>Thymus</td>
<td>Suppression or down-regulation of the immune response</td>
</tr>
<tr>
<td>Cytotoxic T-cells</td>
<td>CD8+</td>
<td>Thymus</td>
<td>MHC class-I restricted; elimination of virus-infected or malignant cells; activated by cytokines (e.g., IFN-γ)</td>
</tr>
<tr>
<td>NK cells</td>
<td>CD16+, CD56+, CD57+</td>
<td>Unknown</td>
<td>Nonspecific lysis of virus-infected or malignant cells; activated by cytokines (e.g., IL-2, IFN-γ)</td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
<td>Bone marrow</td>
<td>Delayed type hypersensitivity; activated by cytokines (e.g., IFN-γ); Ag presentation; production of IL-1; aids in T-cell proliferation</td>
</tr>
</tbody>
</table>

Key: Ag, antigen; CD, cluster of differentiation; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer.
Modulation of the Cellular Immune Response via the SNS

Williams, Snyderman, and Lefkowitz (1976) provided initial evidence that lymphocytes express adrenergic receptors. Subsequent studies have found these adrenergic receptors to be primarily of the α2 subtype, although evidence also exists for the β2 subtype (Plaut 1987). Such findings provide an important pharmacological basis for neuroendocrine activation. However, different subsets of lymphocytes appear to have a greater density of adrenergic receptors and hence may be more susceptible to influences from the SNS. For instance, the density of β-adrenergic receptors is greater on CD8+ T-cells and NK cells than on CD4+ T-cells (Khan et al. 1986; Maisel et al. 1989, 1990; Van Tijt et al. 1990). These data are consistent with studies reporting greater increases in CD8+ T-cells and NK cells in the periphery following infusions of EPI or during exercise (Crary et al. 1983a, b; Landmann et al. 1983; Maisel et al. 1990; Murray et al. 1992; Tvede et al. 1993; Van Tijt et al. 1990). It should be noted, however, that a sizable percentage of NK cells (i.e., 30%-50%) also possess low-density CD8+ molecules. In fact, Scheldowski and colleagues (1996) used more comprehensive staining techniques and found that the increase in CD8+ cells was primarily the result of increases in NK cells with such CD8+ molecules.

There appear to be relatively direct and indirect mechanisms by which the SNS may influence cellular immunity. Felten and colleagues have shown that sympathetic nerve fibers innervate both primary and secondary lymphoid organs (Felten et al. 1987; Felten & Felten 1991; Williams et al. 1981), providing a direct mechanism by which the SNS may influence aspects of cellular immunity. In fact, Felten and Olschowka (1987) found sympathetic contacts between SNS fibers and splenic lymphocytes. Destruction of lymphoid sympathetic fibers via treatment with 6-hydroxydopamine appears to potentiate immune responses to Ag. These observations have led some to argue that the SNS exerts a tonic inhibitory influence on lymphoid immune processes.

A relatively indirect way in which the SNS may influence immunity is via hormones from the adrenal medulla, particularly EPI. In vivo infusions of EPI result in decreases in the proliferative response to mitogens and increases in NK cell activity, an effect that appears primarily mediated by a β2 adrenergic mechanism (Nemoto, Karasawa, & Uehara 1994; Scheldowski et al. 1993, 1996; Van Tijt et al. 1990). One partial explanation for the decreased proliferative response to mitogens and increased NK cell activity is differences in cell trafficking during SNS activation (Crary et al. 1983b; Tvede et al. 1993). For instance, there may be a lower number of CD4+ T-cells and a higher number of NK cells following SNS activation and this may account, in part, for the decreased proliferative response of peripheral blood leukocytes (PBLs). A more complicated pattern of

**Modulation of the Cellular Immune Response via the HPA Axis**

Early studies provided initial evidence for the importance of the HPA axis on the cellular immune response. For instance, hypotalamic lesions inhibited delayed skin hypersensitivity and increased survival time from anaphylactic shock (Jankovic & Isakovic 1973; Korneva & Khai 1963; Luparello, Stein, & Park 1964; Stein, Schiavi, & Camerino 1976). Furthermore, administration of HPA hormones (e.g., cortisone or ACTH) into rabbits and mice increased the survival time of skin grafts, suggesting an inhibition of the cellular immune response involved in graft rejection (Billingham, Krohn, & Medawar 1951; Medawar & Sparrow 1956).

Subsequent research has documented functional receptors for CRH, ACTH, and glucocorticoids on lymphocytes and macrophages (Clarke & Bost 1989; Crabtree, Munck, & Smith 1980a,b; Smith et al. 1987; Webster et al. 1990; Werb, Foley, & Munck 1978). As noted earlier, recent studies also suggest that lymphocytes produce hormones such as ACTH and prolactin (Harbour-McMenamin, Smith, & Blalock 1985; Sabjarwal et al. 1992; Smith & Blalock 1981; Smith et al. 1986). Although the significance of such hormonal production is unclear, theoretically these hormones may act in either an autocrine or paracrine fashion during an immune response (Blalock 1989; Sabjarwal et al. 1992).

The major influence of HPA hormones on cellular immune processes appears to be inhibitory (Munck & Guyre 1991). In vivo infusions of HPA hormones tend to decrease the absolute number of lymphocytes in circulating blood, an effect that appears to reflect a transitory redistribution of lymphocytes into lymphoid compartments (Cupps & Fauci 1982). At higher concentrations, however, glucocorticoids may lead to apoptosis of T-cells (Brunetti et al. 1995). Accompanying the alterations in lymphocyte counts is a decrease in the proliferative response following in vivo administrations of HPA hormones (Clarke et al. 1977; Fauci & Dale 1974). Glucocorticoids appear to exert part of their effects on the immune response by inhibiting aspects of Ag presentation (Baus et al. 1996; Moser et al. 1995).

In vitro studies have provided converging evidence for a direct inhibitory influence of HPA hormones, since preincubation of PBLS with glucocorticoids tends to decrease the proliferative response to mitogens as well as NK cell activity (Gatti et al. 1987; Holbrook, Cox, & Horner 1983; Parrillo & Fauci 1978; Pedersen & Beyer 1986; Wiegers et al. 1993, 1994). These effects were blocked by the specific glucocorticoid receptor antagonist RU-486 (Wiegers et al. 1993, 1994).

HPA hormones may indirectly suppress in vivo cellular immune function in at least two ways. Central administration of CRH reliably decreases the proliferative response to mitogens (Johnson et al. 1994; Labeur et al. 1995) and splenectomized NK cell activity (Irwin et al. 1989). Although central CRH activates the HPA axis, it also activates the autonomic nervous system (ANS), and the influence of central CRH on splenic NK cell activity appears to be mediated by activation of the ANS (Irwin et al. 1989; Irwin, Hauger, & Brown 1992). A possible explanation for these effects is changes in cell trafficking in response to SNS hormones as NK cells are released from lymphoid compartments into the periphery (Grzyb et al. 1983b).

HPA hormones also appear to modulate cytokine production (Munck & Guyre 1991; Munck, Guyre, & Holbrook 1984). The cytokines IL-2 and IFN-γ enhance the cytolytic activity of NK cells (Dinarello & Mier 1987). Note in particular that HPA hormones such as ACTH appear to inhibit the synthesis of both IL-2 and IFN-γ (Arya, Wong-Staal, & Gallo 1984; Johnson et al. 1984; Kelso & Munck 1984).

**Modulation of the Cellular Immune Response via Opioids**

Opium addicts are more at risk for the development of infectious diseases (Tubaro et al. 1983). One explanation for such findings is the possibility that opioids may have an inhibitory influence on immune function. Indeed, early evidence suggested the presence of opioid receptors on cells of the immune system. Wybran and colleagues (1979) found that in vitro incubation of PBLS with morphine was associated with a decrease in the percentage of active T-cells, an effect that was blocked by pretreatment with naltrexone. Subsequent studies appear to have characterized diverse subclasses (e.g., δ, κ, μ) of opioid receptors on cells of the immune system (Carr et al. 1988, 1989; Mehrishi & Mills 1983; for reviews see Carr 1991; Carr, Rogers, & Weber 1996; Sibinga & Goldstein 1988). B-lymphocytes also appear to secrete β-endorphin-like hormones, a process that depends on the secretion of IL-1 from monocytes (Kavelaars, Ballieux, & Heijnen 1989, 1990; Loloj et al. 1984).

Given the diverse opioid receptors identified on lymphocytes, it is perhaps predictable that the influence of the opioids on cellular immunity would be complex. Such data were foreshadowed by the early study from Wybran et al. (1979), who found opposing in vitro effects of morphine and met-enkephalins on the percentage of active T-cells. In general, in vitro effects of β-endorphins have been a decrease in the proliferative response of PBLS to phytohemagglutinin (PHA) (McCain et al. 1982) and an increase in the proliferative response of splenic lymphocytes to PHA and Concanavalin A (Con A) (Gilman et al. 1982; Shahabi, Heagy, & Sharp 1996). Moreover, the effects just reported were not blocked by an opioid receptor.
antagonist (e.g., naloxone). It is interesting that Shahabi et al. (1996) found that the increased response of splenic lymphocytes to Con A was blocked by a δ-opiate receptor antagonist but not by a μ-opiate receptor antagonist. These data suggest that distinct receptor subclasses may be responsible for some of the heterogeneity in prior in vitro studies of opioid hormones.

In vivo studies suggest that infusion of morphine or implantation of morphine pellets has been associated with a decrease in the proliferative response to mitogens (Bayer et al. 1990; Bryant, Bernton, & Holaday 1987; Bryant & Roudabush 1990). These effects appear partially antagonized by an opioid antagonist (Bayer et al. 1990; Bryant & Roudabush 1990). However, at least one study found evidence for compartment specificity as blood and splenic lymphocyte proliferation, but not mesenteric lymph node lymphocyte proliferation, were decreased by in vivo administrations of morphine (Lysle et al. 1993). A subsequent study by Fecho, Dykstra, and Lysle (1993) reported that the decrease in splenic lymphocyte proliferation to Con A was blocked by β-antagonists, suggesting SNS mediation of this effect. This mechanism could not account for the decrease in blood lymphocyte proliferation to Con A observed, which led the authors to suggest that hormones of the HPA axis might be mediating the influence of morphine on blood lymphocyte proliferation to mitogens.

There appear to be differential in vivo and in vitro effects of opioids on NK cell activity. Many in vitro studies have found an increase in NK cell activity following incubation with opioids such as β-endorphins, met-enkephalins, and leu-enkephalins (Faith et al. 1984; Kay, Allen, & Morley 1984; Mandler et al. 1986; Mathews et al. 1983). Most of these effects were blocked by the opioid antagonist naloxone or naltrexone. These studies suggest that direct opioid activation of NK cells is associated with a potentiation of NK cell activity. In contrast, in vivo effects of opioid agonists appear to indicate a decrease in splenic NK cell activity that is blocked by naltrexone (Bayer et al. 1990; Fecho et al. 1993; Freier & Fuchs 1994; Lysle et al. 1993; Shavit et al. 1986; Weber & Pert 1989).

Activation of the SNS and HPA are two potential indirect mechanisms that may be responsible for the in vivo effects of morphine on NK cell activity (Fecho et al. 1993). Fecho and et al. (1993) did not find evidence for an SNS mechanism in the morphine-induced decrease in splenic NK cell activity. In comparison, Freier and Fuchs (1994) reported relatively strong evidence that the decrease in splenic NK cell activity via morphine was mediated by hormones of the HPA axis. These researchers found that in vivo morphine administration was associated with increased corticosterone levels. In addition, in vitro incubation of corticosterone with splenic lymphocytes decreased NK cell activity. More important was the finding that RU-486, a glucocorticoid receptor antagonist, blocked the morphine-induced decrease in splenic NK cell activity.

Frieir and Fuchs (1994) argued that morphine activates central opioid receptors, which in turn stimulate the HPA axis. The resulting rise in corticosterone produces the decrease in spleenic NK cell activity.

**Social Context: Psychosocial Implications**

Psychoneuroimmunology as a discipline has the clear potential to inform our understanding of psychosocial processes at multiple levels of analysis. In this section, we review the literature on stress and immunity to highlight the conceptual utility of human PNI research. However, human PNI research requires attention to relatively unique methodological issues related to the immune system. We begin by discussing such methodological issues.

**MEASUREMENT MILIEU**

Depending on the research question, different methodological issues are of import to human PNI research. In many PNI studies, the first question is typically whether conceptually relevant psychosocial processes are related to immune function. Subsequent studies may then address the question of why such relationships occur. For instance, research on stress-induced changes in immune function has clearly established a relationship between psychosocial stressors and immune function (Herbert & Cohen 1993). Research is now characterizing the mechanisms (e.g., hormonal, behavioral) responsible for these associations at different levels of analysis (Daruna & Morgan 1990; Ironson et al. 1997). When possible, the simultaneous collection of such mechanistic data within and across levels of analysis provides an excellent means by which competing hypotheses can be evaluated (Cacioppo & Berntson 1992; Platt 1964).

There are a number of potentially important methodological issues in relating psychosocial processes to immune function that need to be considered in both correlational and experimental designs (see Kiecolt-Glaser & Glaser 1988a for a review). For instance, depressed or distressed individuals are more likely to self-medicate with alcohol or other drugs (Grumbang & Baum 1985), have poorer nutritional status (Gregory & Smeltzer 1983), and have sleep disturbances (Gregory & Smeltzer 1983). These health-related behaviors have definitely been linked to alterations in immune function (Chandra & Newberry 1977; Irwin et al. 1994; Jaffe 1980; Palmblad 1981). An assessment of or screening for these variables is important so that researchers can evaluate the impact of these factors and/or reduce error variance. In many studies, the reduction of error variance is crucial, owing to the measurement error inherent in some immunological assays and the high costs for large-sample human studies. Both of these factors tend to decrease the power of many PNI studies. We next review important methodological factors that warrant
careful consideration in human PNI research. We should note, however, that the potential influence of these factors and hence decisions about design (e.g., exclusion criteria) will depend on one’s research question.

Alcoholic Consumption. Alcohol intake may influence immunity (MacGregor 1986). In our laboratories, we routinely screen individuals who report drinking ten or more alcoholic beverages a week, or who report more than ten alcoholic drinks in the past week using standard equivalents for alcohol (e.g., 5 oz of wine is equivalent to one 12-oz ounce serving of beer or 1 oz of whiskey). This tends to be a conservative exclusionary criterion, given that many substance abusers underestimate their intake (Grunberg & Baum 1985). There are a number of scales for assessing alcohol abuse in the clinical range (e.g., Selzer 1971). The combination of such scales and biological indices of consumption (e.g., mean corpuscular volume) provides a relatively accurate assessment of alcohol abuse (Skinner et al. 1986).

Nutrition. One of the easiest methods for assessing recent nutrition is to examine self-reported weight changes. This method of assessment, however, is relatively insensitive to the nutritional content of the participant’s diet. With the help of a nutritionist, a food diary methodology might be employed for these purposes, but such issues as when individuals report data (e.g., retrospectively or currently) can influence its accuracy and validity (Block 1982). One simple and efficient way to assess nutritional status is by the measurement of certain plasma proteins. Different protein markers can provide information on relatively short- and longer-term nutritional status. For example, plasma transferrin levels have a half-life of about eight days and can provide information on relatively recent nutritional changes. In comparison, plasma albumin levels have a half-life of about 2-3 weeks and provide information on longer-term nutritional status.

Smoking and Caffeine Intake. Both smoking and caffeine consumption have effects on cardiovascular and neuroendocrine function (Chang et al. 1984; Lane 1994). In addition, these health behaviors can modulate stress-induced physiological changes (Lane & Williams 1985; Perkins et al. 1992). However, the assessment of caffeine can be difficult because of differences in brewing procedures, dosage differences, and variable amounts found in foods and over-the-counter drugs (Dews 1984). In our laboratories, we often exclude tobacco users to reduce variability in neuroendocrine and immune measures. We also typically ask individuals to report caffeine intake in an average week, past week, and last 24 hours using a specific standard of comparison (e.g., cup of coffee, tea).

Sleeping Patterns. Irwin et al. (1994) reported that partial sleep deprivation (i.e., 3 A.M. to 7 A.M.) was sufficient to decrease NK cell activity. The sleep-induced decrease in NK cell activity was reversible by one night of regular sleep. These data highlight the importance of assessing sleep patterns in PNI studies (also see Irwin, Smith, & Gillin 1992). In our studies with medical students, we typically assessed sleep patterns in the three nights prior to low-stress periods to compare with the sleep patterns during the examination periods. Although there are usually reliable differences in sleep patterns, the absolute amounts are not large and typically are not related to immunological measures. There are a number of brief sleep assessment scales that might be used in PNI studies (e.g., Buysse et al. 1989; Hoch et al. 1987). For instance, the Pittsburgh sleep quality index (Buysse et al. 1989) assesses sleep quality and disturbances over a one-month interval; it has good diagnostic sensitivity and specificity in distinguishing good and poor sleepers.

Physical Activity. Exercise is associated with transient increases in many neuroendocrine hormones shown to influence immune function. For instance, EPI, NE, and β-endorphins are typically elevated following exercise (Murray et al. 1992; Simon 1991; Tcede et al. 1993). Therefore, it may be important to ask participants to refrain from strenuous exercise just prior to their participation in PNI studies. A related issue is the influence of more regular exercise patterns on longer-term immune alterations. Relatively less data exist on such relationships (Simon 1991). However, several recent interventions with HIV+ populations suggest that aerobic conditioning can attenuate stress-induced alterations in immunity (e.g., LaPerriere et al. 1990) and that aerobic fitness may also influence a quicker recovery from both psychological and physiological stressors (Brooks & Long 1987). The reliable assessment of exercise patterns via self-report measures has been difficult (Laporte, Montoye, & Caspersen 1985). However, the questionnaire reported by Washburn and Montoye (1986) might prove useful in human PNI studies.

Health Status and Medication Use. Acute conditions that might influence immunity should be assessed or screened. For instance, individuals with recent surgery might be excluded because the anesthetics or surgical trauma have adverse effects on immune function (Lukomska et al. 1983). Individuals with a recent episode of an infectious disease are also reasonable to exclude because of short-term alterations in cellular immunity (Lumio et al. 1983).

The potential exclusion of participants with chronic conditions needs to be carefully considered. As much as 86% of older adults have one or more chronic conditions, and such populations are of particular interest to PNI researchers owing to age-related declines in aspects of cellular immunity (Goodwin, Searles, & Tung 1982). Some of these chronic conditions require medication that might influence immunity. For instance, beta blockers appear
to have adverse effects on the in vitro proliferative response to mitogens (Goodwin, Messner, & Williams 1979; Goodwin et al. 1982). These drugs may also influence stress-induced alterations in immunity via modulation of SNS activity. When using such populations it may be useful to exclude participants who are on medications that have direct influences on immune function (e.g., corticosteroid therapy, beta blockers) or to match treatment and control groups based on these medications. One issue that warrants careful consideration is that striving to obtain a relatively healthy or medication-free population may yield subject samples that are less representative of their respective population with increasing age (Krauss 1980; Metter et al. 1992).

**Blood Samples and Laboratory Assays.** If possible, blood should be sampled from participants at approximately the same time of day to control for diurnal variability in some assays. We suggest that matching the exact time of day is probably less important than ensuring that blood samples are taken within the same 1–3-hr period. In addition, the day in which blood is taken and the assay performed can contribute significant sources of variance. The “measurement occasion” can account for up to 85% of the variability of some functional assays (Schleifer et al. 1989). It is thus important that these measurement variables be matched between treatment and control groups. For instance, one would not want to collect all blood draws for depressed individuals on Monday and nondepressed individuals on Friday. Schleifer and colleagues (1993) demonstrated that analysis of partial variance may be a useful statistical tool to control for day-to-day variability in some immune assays.

Another important issue is the length of time that the blood sample is allowed to sit before performing the assay (Fletcher et al. 1987). This is particularly relevant when samples are sent to a commercial laboratory, which may assay some samples immediately or wait up to 24 hours for others in an attempt to aggregate assays and optimize technicians’ time.

In human PNI research, blood is typically drawn from the arm. Depending on the type of assays, 30–60 cc (1–2 oz) of blood is needed. It is therefore important to screen for individuals who may be blood or needle phobics so that fainting, nausea, and dizziness are minimized. When a number of blood samples are necessary over a period of several hours, the use of an indwelling catheter is recommended in order to minimize the physical and emotional stress of repeated venipuncture. Adaptation periods of 30 min or longer are recommended following catheter insertion to accommodate transient alterations in neuroendocrine measures that might influence immunity (Baum & Grunberg 1985).

It is also advisable to buy sufficient quantities of laboratory supplies (e.g., mitogens, media) at the beginning of each study. This decision may have consequences for variability in some immune measures. For instance, in studies we found a tenfold difference in the relative values obtained for IFN-γ using different lots of Con A to stimulate lymphocyte production of cytokines (Glaser et al. 1986, 1987). Of course, such influences can mask as changes over time if the investigator is not sensitive to these issues.

There are additional issues involved in the interpretation of measures of immune function that may be useful to discuss. Many functional assays do not have a “normative” value associated with the assay. Differences in laboratory protocols can easily produce different absolute values for some functional assays. For instance, differences in the time that mitogens are incubated with lymphocytes (e.g., 48 hours vs. 72 hours) can influence the values obtained for such assays. Therefore, standardization within a laboratory is extremely important so that relative differences in immune assays are replicable. There is also no single generally accepted measure of immune function. As a result, the interpretation of a single measure of immune function representing a down-regulation may be difficult to justify. Studies that measure multiple aspects of immune function will be in a stronger position to make such conclusions by examining the pattern of immune changes across assays.

**INTER- AND INTRAINDIVIDUAL PROCESSES AND APPLICATIONS**

There are at least two related areas in which PNI has made significant contributions. As noted earlier, our understanding of immunity at a systems level would be far more rudimentary without consideration of the relationships among the CNS, endocrine, and immune systems. In particular, PNI has tremendous implications for our understanding of how psychosocial processes might influence health outcomes via immunological mechanisms. Perhaps the most detailed analysis to this point is the possibility that stress may influence health via alterations in immunity. In the following section, we review human studies on the effects of stress on aspects of the cellular immune response and its implications for health. We first discuss in detail laboratory paradigms of immune alterations to acute psychological stress. We then examine studies linking longer-term or chronic stress to immunity and the health implications of such psychosocially mediated immune alterations.

**Acute Laboratory Stress and Immunity**

The use of standardized tasks for eliciting cardiovascular reactivity in the laboratory has served as a model for PNI researchers, who have examined short-term immune changes to psychological stress. Such laboratory paradigms have demonstrated reliable changes in physiological function that appear to provide information on an individual
<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants (Age, in Years) [Stressor]</th>
<th>Design</th>
<th>Immune Measures</th>
<th>Neuroend.-Immune Interactions</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landmann et al.</td>
<td>11 men, 4 women (Mdn age = 20) [8 min Stroop task]</td>
<td>WS factor: Epoch (pre, post)</td>
<td>B-cells, CD3, CD4, CD8, granulocytes, monocytes, NK cells</td>
<td>Yes</td>
<td>Inc. NK cells, B-cells, monocytes to stressor. Neg. correlation between E/A and ratio of helper/suppressor cells at rest and after stress</td>
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<td></td>
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<td>BS factor: Controllability (cont., no-cont.)</td>
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<tr>
<td>Weisse et al.</td>
<td>22 men (M age = 28) [30 min shock w/ noise]</td>
<td>WS factor: Epoch (pre, post)</td>
<td>B-cells, CD3, CD4, CD8, granulocytes, monocytes, Con A, PHA</td>
<td>No data collected</td>
<td>Cont. group had greater dec. in monocytes and Con A than no-cont. group</td>
</tr>
<tr>
<td></td>
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<td>BS factor: Controllability (cont., no-cont.)</td>
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<tr>
<td>Brosschot et al.</td>
<td>12 men, 13 women (M age = 23) [30 min uncont. interpersonal stress]</td>
<td>WS factor: Epoch (pre, post)</td>
<td>CD4, CD8, NK cells</td>
<td>No data collected</td>
<td>Stress associated with dec. percent CD4 cells and inc. percent NK cells.</td>
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<td>BS factor: Group (stress, no stress)</td>
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<tr>
<td>Manuck et al.</td>
<td>25 men (ages 18–30) [20 min Stroop and math task]</td>
<td>WS factor: Epoch (pre, post)</td>
<td>CD4, CD8, B-cells, PHA</td>
<td>No data collected</td>
<td>In response to stress, high-SNS reactors had greater dec. in PHA and inc. in CD8 than low-SNS reactors</td>
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<tr>
<td></td>
<td></td>
<td>BS factors: Group (stress, no stress); SNS reactor (low, high)</td>
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<tr>
<td>Naliboff et al.</td>
<td>12 younger women (M age = 31), 11 older women (M age = 71) [12 min math or neutral film]</td>
<td>WS factors: Epoch (pre, post); Session (stress, no stress film)</td>
<td>B-cells, CD3, CD4, CD8, NK cells, NK cell activity</td>
<td>No data reported</td>
<td>Inc. CD8, NK cells to stressor. Younger group showed greater inc. in NK cell activity to stress than older group</td>
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<td>BS factor: Age (younger, older)</td>
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<tr>
<td>Bachen et al.</td>
<td>44 men (ages 19–25) [21 min Stroop task]</td>
<td>WS factor: Epoch (pre, post)</td>
<td>B-cells, CD3, CD4, CD8, NK cells, PHA</td>
<td>Yes</td>
<td>Stress group showed dec. CD4, PHA and inc. CD8, NK cells. Qualitative analyses suggest that stress-induced changes in CD8 and PHA were more pronounced in high-SNS than low-SNS reactors</td>
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<td></td>
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<td>BS factor: Group (stress, no stress)</td>
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<tr>
<td>Brosschot et al.</td>
<td>86 men (M age = 41) [30 min uncont. interpersonal stress]</td>
<td>WS factor: Epoch (pre, post)</td>
<td>CD3, CD4, CD8, HLA-DR, leukocytes, monocytes, NK cells, AG, PHA, PWM</td>
<td>No data collected</td>
<td>Stress group had inc. CD8, NK cells.</td>
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<tr>
<td></td>
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<td>BS factor: Group (stress, no stress)</td>
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<tr>
<td>Study</td>
<td>Gender/Age/Condition</td>
<td>Design Variables</td>
<td>Outcomes</td>
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<tr>
<td>Knapp et al.</td>
<td>10 men, 10 women (ages 18–30)</td>
<td>WS factors: Epoch (pre, post); Emotion (pos., neg.)</td>
<td>CD3, CD4, CD8, lymphocytes, monocytes, Con A, PHA, PWM, NK cell activity</td>
<td></td>
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<tr>
<td>(1992)</td>
<td>[40 min recall of maximally pos. or neg. experience]</td>
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<td>Yes</td>
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<td>Neg. and pos. recall associated with dec. Con A and PHA</td>
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<td>During neg. condition, HR reactivity negatively related to</td>
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<td>PHA response to stress</td>
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<td>During neg. condition, HR reactivity positively related to</td>
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<td>number of lymphocytes and NK cell activity in response to stress</td>
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<td>During neg. condition, SBP reactivity positively related to</td>
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<td>NK cell activity in response to stress</td>
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<tr>
<td>Sieber et al.</td>
<td>53 men (ages 18–26)</td>
<td>WS factor: Epoch (pre, post); BS factor: Group</td>
<td>CD3, CD4, CD8, NK cells, monocytes, lymphocytes, NK cell activity</td>
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<tr>
<td>(1992)</td>
<td>(20 min noise)</td>
<td>(esc. noise, inesc. noise-resp., inesc. noise-no resp., no noise)</td>
<td>No data collected</td>
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<td>Inesc. noise-no resp. associated with NK cell activity compared with</td>
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<td></td>
<td>other groups</td>
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<tr>
<td>Zakowski et al.</td>
<td>29 men (M age = 31)</td>
<td>WS factor: Epoch (pre, post); BS factor: Group</td>
<td>Granulocytes, monocytes, lymphocytes, IL-1, IL-2, Con A, PHA</td>
<td></td>
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<tr>
<td>(1992)</td>
<td>(30 min view and recall of &quot;gruesome&quot; film)</td>
<td>(stress, no stress)</td>
<td>Yes</td>
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<td>Stress group showed dec. in Con A</td>
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<td>High-SBP reactors (film and recall periods) showed smaller</td>
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<td>Con A response to stress</td>
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<td>High-SBP and -DBP reactors (film period) showed dec.</td>
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<td>Con A response to stress</td>
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<td>High-SBP reactors (recall period) showed greater Con A response to stress</td>
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<tr>
<td>Stone et al.</td>
<td>43 men (M age = 23)</td>
<td>WS factor: Epoch (pre, post); BS factor: Group</td>
<td>Con A, PHA</td>
<td></td>
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<tr>
<td>(1993)</td>
<td>(20 min Stroop and math tasks)</td>
<td>(low ANS, high ANS, no stress)</td>
<td>Yes</td>
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<td>Stress group showed dec. in Con A</td>
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<td>High-ANS reactors group had greater dec. in Con A to stress than low-ANS</td>
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<td>reactors and no-stress groups</td>
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<tr>
<td>Benschop et al.</td>
<td>31 men (M age = 23)</td>
<td>WS factor: Epoch (pre, post); BS factor: Blockade</td>
<td>CD3, CD4, CD8, NK cells, lymphocytes, PHA, NK cell activity</td>
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<tr>
<td>(1994)</td>
<td>(20 min tone avoidance and memory search tasks)</td>
<td>(propanolol, placebo)</td>
<td>Yes</td>
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<td>Placebo group showed greater stress-induced inc. in NK cells and NK cell</td>
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<td>activity than propanolol group</td>
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<tr>
<td>Futterman et al.</td>
<td>16 men actors (M age = 35); 8 men, 1 woman non-actor (M age = 29)</td>
<td>WS factors: Epoch (pre, post); BS factor for baseline</td>
<td>CD3, CD4, CD8, NK cells, NK cell activity, PHA</td>
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<tr>
<td>(1994)</td>
<td>[20 min mood induction]</td>
<td>baseline only: Group (Actor, non-actor/actress)</td>
<td>Yes</td>
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<td>Overall, mood manipulation associated with inc. CD8, NK cells, and NK cell</td>
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<td>activity</td>
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<td>Previous effects eliminated while statistically controlling</td>
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<td>for HR reactivity (except CD57 cells)</td>
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<td>Pos. mood associated with inc. in PHA and neg. mood associated with dec.</td>
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<td></td>
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<td>in PHA (high dose)</td>
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<thead>
<tr>
<th>Authors</th>
<th>Participants (Age, in Years) [Stressor]</th>
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<th>Immune Measures</th>
<th>Neuroend.–Immune Interactions</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbert et al.</td>
<td>22 men, 19 women (M age = 22) [21 min Stroop task]</td>
<td>WS factor: Epoch (pre, 5-min task, post) BS factor: Group (low card. reactor, high card. reactor, no stress)</td>
<td>B-cells, CD4, CD8, NK cells, PHA</td>
<td>Yes</td>
<td>Stress group had greater inc. in CD8 and NK cells and greater dec. in PHA than no-stress group High card. reactors in stress group had greater inc. in CD8 and NK cells and greater dec. in PHA than low reactors in stress group or no-stress group</td>
</tr>
<tr>
<td>Sgoutas-Emech et al.</td>
<td>Prescreen: 44 men (ages 18–31) Main study: 22 low- and high-HR reactors during prescreen [Prescreen: 6 min speech task Main study: 12 min math task]</td>
<td>WS factor: Epoch (pre, post) BS factor: HR reactor (low, high)</td>
<td>CD4, CD8, NK cells, Con A, PHA, NK cell activity</td>
<td>Yes</td>
<td>Stressor resulted in dec. Con A and inc. CD8, NK cells, and NK cell activity High-HR reactors showed greater stress-induced inc. in cortisol and NK cell activity than low-HR reactors</td>
</tr>
<tr>
<td>Bachen et al.</td>
<td>52 men (ages 18–30) [18 min Stroop, math, and speech tasks]</td>
<td>WS factor: Epoch (pre, post) BS factor: Group (stress, no stress); Blockade (labetalol, placebo)</td>
<td>B-cells, CD4, CD8, NK cells, Con A, PHA, NK cell activity</td>
<td>Yes</td>
<td>Placebo stress group had greater inc. in NK cells and NK cell activity and greater dec. in Con A and PHA than other three groups</td>
</tr>
<tr>
<td>Benschop et al.</td>
<td>70 men (M age = 41) [30 min interpersonal stressor]</td>
<td>WS factor: Epoch (pre, post) BS factor: Group (stress, no stress)</td>
<td>NK cells</td>
<td>Yes</td>
<td>Stress associated with inc. NK cells HR, SBP, and DBP reactivity associated with inc. NK cells in both stress and no-stress conditions</td>
</tr>
<tr>
<td>Cacioppo et al.</td>
<td>22 women (M age = 67) [12 min math and speech tasks]</td>
<td>WS factor: Epoch (pre, 6-min task, post)</td>
<td>CD3, CD4, CD8, NK cells, Con A, PHA, NK cell activity</td>
<td>No data reported</td>
<td>Stressor led to dec. in percent of CD4 and Con A; inc. in percent of CD8, NK cells, and inc. NK cell activity</td>
</tr>
<tr>
<td>Caggiula et al.</td>
<td>29 women in follicular stage (ages 20–30) [11 min mirror tracing, speech, and Stroop tasks]</td>
<td>WS factor: Epoch (pre, post) BS factor: Group (stress, no stress)</td>
<td>B-cells, CD3, CD4, CD8, IL-1β prod., IL-2 prod., IgG prod., IgM prod., granulocytes, monocytes, lymphocytes, NK cells, PHA, PWM, NK cell activity</td>
<td>See Matthews et al. (1995)</td>
<td>Stress associated with dec. in percent CD4, IgM prod., PHA, and PWM Stress associated with inc. in lymphocytes, B-cells, CD3, NK cells, and NK cell activity</td>
</tr>
<tr>
<td>Study</td>
<td>Gender</td>
<td>Age Range</td>
<td>Task</td>
<td>Stressor</td>
<td>Immune Response</td>
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<tr>
<td>Marsland et al. (1995)</td>
<td>30 men (ages 18–30)</td>
<td>2 sessions (2 weeks apart) of 5 min speech task</td>
<td>WS factors: Epoch (pre, post); Session (1, 2)</td>
<td>B-cells, CD3, CD4, CD8, NK cells, Con A, PHA</td>
<td>No data reported</td>
</tr>
<tr>
<td>Matthews et al. (1995)</td>
<td>19 women (ages 20–35)</td>
<td>11 min mirror tracing, speech, and Stroop tasks</td>
<td>WS factors: Epoch (pre, post); BS factor: SNS reactor (low, high)</td>
<td>B-cells, CD3, CD4, CD8, IL-1β prod., IL-2 prod., IgG prod., IgM prod., granulocytes, monocytes, lymphocytes, NK cells, PHA, PWM, NK cell activity</td>
<td>Yes</td>
</tr>
<tr>
<td>Mills et al. (1995a)</td>
<td>24 men (M age = 30)</td>
<td>2 sessions (6 weeks apart) of 6 min speech task</td>
<td>WS factors: Epoch (pre, post); Session (1, 2)</td>
<td>CD3, CD4, CD8, NK cells</td>
<td>No data collected</td>
</tr>
<tr>
<td>Mills et al. (1995b)</td>
<td>20 women (M age = 31)</td>
<td>2 sessions (6 weeks apart) of 6 min speech task</td>
<td>WS factors: Epoch (pre, post); Session (1, 2)</td>
<td>CD3, CD4, CD8, NK cells</td>
<td>No data reported</td>
</tr>
<tr>
<td>Naliboff et al. (1995a)</td>
<td>20 men (M age = 28)</td>
<td>12 min math task</td>
<td>WS factors: Task (math, video); Drug (naloxone, saline), BS factor: Card. reactor (low, high)</td>
<td>B-cells, CD3, CD4, CD8, NK cells, NK cell activity</td>
<td>Yes</td>
</tr>
<tr>
<td>Naliboff et al. (1995b)</td>
<td>20 men (M age = 29)</td>
<td>Role-play task (M = 6 min)</td>
<td>WS factors: Epoch (pre, post); Condition (stress, no stress)</td>
<td>B-cells, CD3, CD4, CD8, NK cells, NK cell activity, adjusted NK cell activity</td>
<td>Yes</td>
</tr>
<tr>
<td>Uchino et al. (1995)</td>
<td>23 women (M age = 19)</td>
<td>12 min math task</td>
<td>WS factor: Epoch (pre, post)</td>
<td>Con A, PHA, NK cell activity</td>
<td>Yes</td>
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(continued)
### TABLE 2 (continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants (Age, in Years) [Stressor]</th>
<th>Design</th>
<th>Immune Measures</th>
<th>Neuroend.–Immune Interactions</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delahanty et al. (1996)</td>
<td>31 men (M age = 29) [6 min math or 6 min cold pressor task]</td>
<td>WS factor: Epoch (pre, instruction, 2-min task, 5-min post) BS factor: Group (math, cold pressor, no stress)</td>
<td>Con A, PWM, NK cell activity</td>
<td>Yes</td>
<td>Math group showed inc. of NK cell activity during task while other groups did not change significantly. Math and cold pressor groups showed dec. in Con A and PWM during task that recovered faster in cold pressor group (Con A). HR and DBP reactivity predicted inc. NK cell activity to stress. HR reactivity predicted dec. peak Con A response to task.</td>
</tr>
<tr>
<td>Gerritsen et al. (1996)</td>
<td>Study 1: 17 men, 22 women (M age = 23); Study 2: 23 men, 36 women (M age = 21) [30 min speech preparation and 5 min speech to “expert” audience]</td>
<td>Study 1: WS factor: Epoch (pre, post) Study 2: WS factor: Epoch (pre, prep, post) BS factor: Group (stress, no stress)</td>
<td>B-cells, CD3, CD4, CD8, HLA-DR, NK cells, NK cell activity, Pdb/iona, FHA, PWM</td>
<td>No data reported</td>
<td>In both studies, stress associated with inc. NK cells and NK cell activity (relative to no stress in study 2). In both studies, stress associated with dec. percent CD4 cells (relative to no stress in study 2).</td>
</tr>
<tr>
<td>Liang et al. (1997)</td>
<td>24 right-handed boys (ages 14–16) [5 min scanning task, 8 min social competence interview]</td>
<td>WS factor: Epoch (pre, post)</td>
<td>B-cells, CD3, CD4, CD8, NK cells, NK cell activity, PWM, TT</td>
<td>No data reported</td>
<td>Stressor associated with inc. B-cells, CD3, CD4, TT</td>
</tr>
</tbody>
</table>

Key: AG, antigen cocktail; ANS, autonomic nervous system; BS, between-subjects; card., cardiovascular; CD, cluster of differentiation; Con A, concanavalin A; cont., controllable; DBP, diastolic blood pressure; dec., decrease(d); EPI, epinephrine; esc., escapable; HR, heart rate; HLA, human leukocyte antigen; IgG, immunoglobulin gamma; IgM, immunoglobulin mu; IFN, interferon; IL, interleukin; inc., increase(d); inesc., inescapable; M, mean; Medn, median; min, minute; NE, norepinephrine; neg., negative; neuroend., neuroendocrine; NK, natural killer; Pdb/iona, phorbol dibutyrate/ionomycin; PEP, pre-ejection period; PHA, phytohemagglutinin; pos., positive; prep, preparation; prod., production; PWM, pokeweed mitogen; resp., response; SBP, systolic blood pressure; SNS, sympathetic nervous system; TT, tetrars toxoid; uncont., uncontrollable; WS, within-subjects.
responses during acute stress. Moreover, high-HR reactors also evidenced increased NK cell activity during stress compared to low-HR reactors (see also Delahanty et al. 1996; Knapp et al. 1992). Analyses of catecholamine responses did not reveal the same pattern of results, suggesting that HR reactivity was serving as a relatively specific marker of HPA activation and may be a second mechanism coordinating aspects of immune changes during acute stress.

Subsequent studies by our laboratories have revealed that the sympathetic substrate of HR reactivity (i.e., pre-ejection period) but not the parasympathetic substrate (i.e., respiratory sinus arrhythmia) was specifically associated with stress-induced increases in NK cell activity (Cacioppo et al. 1995; Uchino et al. 1995; see Cacioppo et al. 1994 for validation of these autonomic measures). We also found that blood pressure responses to acute stress predicted changes in NK cell activity (see also Delahanty et al. 1996; Knapp et al. 1992) and hypothesized that cardiac sympathetic activation, as indexed by pre-ejection period (PEP), may influence NK cell activity via SBP reactivity due to mechanical (e.g., increased vascular pressure) or soluble immune factors (Ottaway & Husband 1992). Mediational analyses utilizing a path-analytic model revealed support for this hypothesis (see Uchino et al. 1995).

The association between cardiac sympathetic control and NK cell activity responses to short-term psychological stress were apparently not mediated by the activation of the HPA, as suggested by Sgoutas-Emch et al. (1994). As depicted in Figure 1, the most likely mechanism for short-term immune changes observed in acute laboratory studies appears to be SNS activation. We should note, however, that the potential role of the HPA axis in relatively acute stress should not be ignored, especially in light of the limitations inherent in these studies (e.g., moderate stress levels, short-term duration). In addition, the coactivation of cortisol in high but not low cardiac sympathetic reactors may be a mechanism with significant implication for longer-term immune alterations in chronically stressed individuals. Consistent with the possibility that these laboratory paradigms may provide information on an individual's response to daily hassles and stressors, we found that PEP and cortisol reactivity to acute psychological stress predicted a decline in the T-cell response to an influenza vaccination in older adults (data reported in Cacioppo 1994). As we shall review, these data suggest that activation of the HPA axis may play a relatively larger role in more chronic stress.

**Chronic Stress and Immunity**

Chronic stress may be the result of long-term exposure to stressors. However, according to Baum, O'Keefe, and Davidson (1990) this definition does not account for why relatively short-term events can have long-term consequences (e.g., the Three-Mile Island incident). In such cases, chronic stress may result from lasting perceptions of stress that are driven by ruminative thinking (Baum 1990). Thus, chronic stress may be defined in either fashion, with a "perfect" chronic stressor involving long-term exposure and lasting perceptions of stress (e.g., caregiving for a family member with dementia).


As an exemplar, Kiecolt-Glaser and colleagues (1991) found that long-term caregiving for a family member with AD was associated with lower levels of cellular immunity, as indexed by decreased PBL response to mitogens and increased Ab titers to latent Epstein–Barr virus (EBV), compared with demographically matched control participants. Moreover, these changes did not appear to "rebound" upon termination of the chronic stressor. Caregivers whose family members had been deceased on the average of two years still showed signs of a down-regulated immune response (Esteling et al. 1994). It is important to note that these data do not necessarily indicate that such potentially negative changes in immunity are uniform across individuals. For instance, psychosocial resources such as social support may moderate immune changes in chronically stressed individuals. Kiecolt-Glaser and colleagues (1991) also reported that chronically stressed individuals with low social support showed the most negative alterations in cellular immunity.

Although one should proceed cautiously when generalizing the results of these different operationalizations of chronic stress, it appears that chronic stress is more reliably

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**Figure 1. The mediational influence of the sympathetic nervous system linking acute stress to alterations in immune function.**
related to decreases in functional rather than quantitative measures of cellular immunity (Bartrop et al. 1977; Kiecolt-Glaser et al. 1987a, 1991; Kiecolt-Glaser & Glaser 1995; Jabaraj et al. 1993; Kemeny et al. 1995; Schleifer et al. 1983). As depicted in Figure 2, we propose that although SNS activation may play a role in chronic stress and immunity, the HPA axis may account for a major part of these cellular immune changes. Chronic stress (especially uncontrollable stress) results in HPA activation in both animal and human models (Calabrese, Kling, & Gold 1987; Frankenheuser 1986; Mason 1975; Sapolsky, Krey, & McEwen 1986; Seeman & Robbins 1994), and HPA hormones inhibit many aspects of cell-mediated immunity (Munck & Guyre 1991). Chronic stress may also be linked to a down-regulation of adrenergic receptors that limit SNS influences on immunity (Dimsdale et al. 1994). In comparison, chronic stress has been associated with a down-regulation of hippocampal glucocorticoid receptors that terminate the cortisol response (Sapolsky, Krey, & McEwen 1984). These findings have led to the suggestion that the kinetics of the cortisol response may be extended in chronic stress populations with deleterious consequences (Sapolsky et al. 1986; Seeman & Robbins 1994). However, none of these studies on chronic stress and immunity in humans appears to have directly examined the mediational role of neuroendocrine hormones on these cellular immune changes (see Baron & Kenny 1986).

It is noteworthy that psychosocial interventions appear useful in modulating at least some components of the immune response (Kiecolt-Glaser et al. 1985). These interventions include chronically stressed populations such as cancer patients (Andersen, Kiecolt-Glaser, & Glaser 1994; Fawzy et al. 1990a, b; Kiecolt-Glaser et al. 1985) and HIV+ individuals (LaPerriere et al. 1990). In one of the first studies demonstrating a direct effect of a psychosocial intervention on immunity, Kiecolt-Glaser and colleagues (1983) found that relaxation training increased NK cell activity and decreased Ab titers to latent herpes simplex virus (HSV) in an older adult population. (Ab titers to latent HSV reflect the steady-state expression of the latent virus and the status of the virus-specific T-cell response.) Fawzy and colleagues (1990a, b) evaluated the effects of a six-week structured group intervention that consisted of education, problem-solving skills, and stress management such as relaxation and support in stage-I or -II cancer patients. The structured group intervention was associated with increases in aspects of cellular immunity such as percent NK cells and NK cell activity six months later compared with the control condition. Note especially that a six-year follow-up revealed lower mortality rates in individuals assigned to the group intervention relative to the control condition.

The study by Fawzy and colleagues (1990a, b) suggests that psychosocial alterations in immune function may have significant health consequences. Clearly, questions regarding the biological significance of psychosocially mediated immune alterations in humans is an important area of inquiry for health-related PNI research. Animal models have provided relatively consistent evidence that stressors may influence the development of tumor growth and viral infections (Ben-Eliahu et al. 1991; Bonneau et al. 1991a, b; Habu et al. 1984; Riley 1981; Sklar & Anisman 1981; Visintainer, Volpicelli, & Seligman 1982). In Table 3 we detail recent human studies suggesting that psychosocial factors may result in biologically significant immune changes with health consequences (Cohen, Tyrrell, & Smith 1991; Glaser et al. 1992; Kiecolt-Glaser et al. 1995, 1996). These biological endpoints include viral infections and clinically diagnosed colds (Cohen et al. 1991), vaccination to hepatitis-B and influenza virus (Glaser et al. 1992; Kiecolt-Glaser et al. 1996), and wound healing (Kiecolt-Glaser et al. 1995). All of these studies were prospective designs that included controls for standard demographic variables and health-related behaviors. Thus, although more data are needed, direct evidence is beginning to emerge on the health consequences of psychosocial factors via immunological mechanisms.

**Inferential Context**

### Measurement and Quantification

**Biometrics**

There is no single measure of immune function; yet researchers in the field of PNI have utilized various measures to index its aspects. A distinction has typically been made between quantitative and functional measures of the immune system (Kiecolt-Glaser & Glaser 1988b). Quantitative measures can include percentages of certain immune cells such as helper T-cells, suppressor/cytotoxic T-cells, and NK cells. With the addition of complete blood counts, measures of cell percentages can be converted to absolute counts. The examination of absolute counts is important because they can serve as a marker of disease progression in immunodeficient populations (e.g., HIV+ individuals).

A recent review by Herbert and Cohen (1993) also suggests that psychosocial processes may be more closely related to absolute cell counts than cell percentages. Most importantly, one needs to correct functional measures (e.g., cytokine levels) for number of cells in order to determine if a change in observed function is simply due to a corresponding change in cell numbers.
### TABLE 3. Stress-Associated Immune Modulations: Implications for Health

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants (Age, in Years) [Psychosocial Factor(s)]</th>
<th>Design</th>
<th>Immune Measures (Outcomes)</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al.</td>
<td>154 men, 266 women (M age = 34) [Psychological stress]</td>
<td>Prospective viral challenge (common cold) study Assessment period (pre challenge, post challenge)</td>
<td>Biological infections, clinical colds</td>
<td>Psychological stress associated in a dose–response manner with increased infections and clinical colds, controlling for standard variables and health practices</td>
</tr>
<tr>
<td>Glaser et al.</td>
<td>25 men, 23 women 2nd-year medical students (M age = 23) [Anxiety, perceived stress, social support]</td>
<td>Prospective Hep-B vaccination study Assessment period (first injection of Hep-B, second injection 1 month later, and booster injection at 6 months)</td>
<td>Ab titers to Hep-B, T-lymphocyte response to Hep-B (Seroconversion)</td>
<td>No participant was Ab positive for Hep-B before vaccination. Participants who seroconverted after first inoculation were less anxious and stressed than later seroconverters. Statistical controls for Ab titers and T-lymphocyte response during second inoculation revealed that stress, anxiety, and social support positively associated with a summary index of Ab titers and T-lymphocyte response to Hep-B during third inoculation.</td>
</tr>
<tr>
<td>Kiecolt-Glaser et al.</td>
<td>13 AD caregivers (M age = 62), 13 matched controls (M age = 60) [Chronic stress of caregiving]</td>
<td>Prospective wound healing study Assessment period (1 week post punch biopsy, every 2–8 days until wound healed)</td>
<td>IL-1β (Number of days to complete wound healing; size of wound)</td>
<td>Complete wound healing took almost 24% longer in caregivers (48 days) than controls (39 days); Caregivers had lower IL-1β levels in response to stimulation than controls. Differences in caregivers and controls did not appear to be a result of health-related behaviors.</td>
</tr>
<tr>
<td>Kiecolt-Glaser et al.</td>
<td>14 men, 18 women AD caregivers (M age = 73), 14 men, 18 women matched controls (M age = 73) [Chronic stress of caregiving]</td>
<td>Prospective influenza vaccination study Assessment period (pre inoculation, 3.5–6 week post inoculation, 3 month post inoculation – successful responders only, 6 month post inoculation – successful responders only)</td>
<td>CD3⁺, CD4⁺, CD8⁺, macrophages (Monocytes, IL-1β prod., IL-6 prod., influenza-specific IL-2 response)</td>
<td>Caregivers and controls had comparable influenza vaccine histories and baseline levels of Ab titers. Caregivers were less likely to respond successfully to vaccination than controls; this difference was especially evident in participants over 70 years old. IL-1β and IL-2 levels were lower in successful responding caregivers than controls at 3- and 6-month follow-up. Differences in caregivers and controls did not appear to be a result of health-related behaviors.</td>
</tr>
</tbody>
</table>

**Key:** Ab, antibody; AD, Alzheimer's disease; CD, cluster of differentiation; Hep-B, Hepatitis B; IL, interleukin; M, mean; NK, natural killer; prod., production.

From the white blood cells, immune cell types are identified using commercially available monoclonal Abs. Specific monoclonal antibodies are used for the identification of certain “markers” on cell surfaces. T-cells can be identified by the CD3⁺ molecule that is present on the T-cell receptor. Subsets of T-cells can also be identified: CD4⁺ cells distinguish helper T-cells, whereas CD8⁺ cells distinguish suppressor/cytotoxic T-cells. Natural killer cells
may also be quantified as CD3<sup>+</sup>, CD16<sup>+</sup>, or CD56<sup>+</sup>. Quantification of these specific cell types can be performed by flow cytometry.

Cellular immune function is also widely studied from a functional perspective through the use of in vitro methods. One common measure is the blastogenic response of lymphocytes to mitogens (e.g., Con A, PHA) or specific (e.g., viral) Ag. In these assays, lymphocytes and mitogen/Ag are incubated together for a period of time. As lymphocytes proliferate in response to the mitogen, the use of radioactive thymidine to measure the level of DNA in the dividing cells allows the measurement of lymphocyte proliferation. Blastogenesis provides an in vitro model for lymphocyte proliferation in response to pathogens; greater proliferation is typically interpreted as a better cellular immune response. Another common functional assay is NK cell activity, which measures the ability of NK cells to lyse a target cell (e.g., tumor cell). In this assay, the target cells are labeled with <sup>51</sup>Cr and incubated with NK cells (PBLs). As the NK cells lyse the target cells, <sup>51</sup>Cr is released into solution; NK cell activity is determined by the amount of radioactivity of the sample after incubation. Greater NK cell activity is also thought to represent a better immune response.

One of the hallmarks of immunity is “memory” - whereby pathogens eradicated from the host are met with a more effective immune response upon subsequent exposure. This memory is possible owing to the presence of memory T- and B-cells, which may survive for long periods of time. However, some pathogens have complex strategies that help them to avoid elimination from the body. Latent herpes viruses (e.g., EBV, HSV) avoid elimination by going latent and “hiding” - relatively inactive - in certain cells. The exposed individual is infected for life but the cellular immune response is usually successful at keeping the virus in check. However, individuals with compromised cellular immune responses (e.g., HIV+ populations and patients on immunosuppressive therapies) may experience reactivation of one or more of these latent viruses. In such cases, Ab titers to the virus provide a measure of the virus-specific cellular immune response. For these measures, increased Ab titers to latent viruses suggest poorer cellular immunity because the cellular immune response is relatively less effective in controlling the steady-state expression of latent viruses. Ab titers to latent viruses appear to be among the more sensitive measures in PNI research to psychosocial influences (Herbert & Cohen 1993; Kiecolt-Glaser & Glaser 1995).

Thus far we have limited our discussion to the more common approaches to measuring the cellular immune response in human PNI research. There are at least two related measurement issues that deserve attention, given recent trends. One general issue in PNI research relates to the problematic interpretation of any single measure of immune function (e.g., decreases in response of PBLs to Con A, production of INF-γ by PBLs in vitro) as representing a down-regulation of immune function. It is possible that a composite of measures of cellular immunity may provide a better overall characterization of an individual's immune status with implications for health. According to this model, the separate measures combine to influence the composite, so that changes to one aspect may have cascading consequences. For instance, Kiecolt-Glaser and colleagues (1991) found that chronically stressed caregivers of AD patients - caregivers who showed the largest decrements in immunity on a composite measure conceptually linked to cellular immune responses (i.e., Ab titers to latent EBV, response of PBLs to Con A and PHA) - were low in social support. Of course, if one is attempting to model potential mechanisms, a conceptual disaggregation of the composite may provide insight into what stage(s) of the immune response is influenced by psychosocial processes.

In order to demonstrate the biological significance of psychosocial processes, recent human PNI research is beginning to examine the primary and secondary immune responses to antigens. One typically has no prior immunologic exposure to a “new” Ag, whereas one typically has a more vigorous immune response to additional exposure to the same Ag (see the studies listed in Table 3). It is clear that cytokines play an important role in directing and modulating aspects of cellular immunity to such challenges (Detrick & Hooks 1997; Dinarello & Mier 1987). Cytokine production can typically be measured via biosays or immunoassays such as ELISA (Detrick & Hooks 1997).

Researchers in PNI are also starting to investigate psychosocial modulation of cytokines such as IL-2 and INF-γ in order to model potential mechanisms. For instance, Kiecolt-Glaser and colleagues (1996) examined the influence of chronic stress on immune responses to an influenza virus vaccination in older adults. Results revealed that caregivers had a poorer Ab response to vaccination than demographically matched control participants. An examination of cytokine profiles revealed that IL-1β and IL-2 responses to the vaccination were lower in caregivers than controls. It is important to note that both cytokines play a key role in T-cell activation. In addition, IL-2 enhances the cytolytic function of cytotoxic T-cells. Thus, Kiecolt-Glaser and colleagues (1996) found evidence for the potential pathways responsible for the poorer Ab response in these chronically stressed caregivers.

**Psychometrics**

An important issue to consider in PNI research is the psychometric properties of the immunological assessments. In this regard, it is conceptually important to distinguish between measurement reliability and temporal stability. Measurement reliability refers to the accurate assessment of the physiological state at one point in time. In comparison, temporal stability refers to a dispositional
characterization of physiological function (i.e., stability of the physiological assessment across different situations and occasions). Adequate measurement reliability is necessary but not sufficient for temporal stability. The distinction between measurement reliability and temporal stability is important for at least two reasons. First, it bears on the replicability and generalizability of research findings across occasions, people, and places. Second, if psychosocial factors are to have effects on disease processes with a long-term etiology, the physiological assessments should be characterized by adequate temporal stability. The assessment context (e.g., specific tasks), population (e.g., phobics), and techniques (e.g., specificity of tracers in radioimmunoassay) may all influence an individual difference assessment of cellular immune function. As an example, a needle stick is often associated with relatively short-term elevations in catecholamines. Because of the measurement reliability of current techniques (Baum & Grunberg 1995), the catecholamine changes due to venipuncture would be accurately assessed at that moment. However, this may be a poor index of an individual’s catecholamine response across time and situations.

The measurement reliability of immunological data varies across assays and laboratories. Issues such as the day on which an individual’s immunological data are analyzed can contribute significant variance for some assays. Considerable work has been done to assure the measurement reliability of some tests across laboratories and times – for example, percentages of T-lymphocytes and subpopulations (Gelman et al. 1993; Paxton et al. 1989; Schenker et al. 1993). Similarly, studies performed after implementation of quality control procedures to establish reliability and reduce daily variability of NK cell lysis show that NK cell activity is also characterized by adequate measurement reliability (Wieslies & Herberman 1994). Only a handful of studies have examined the temporal reliability of common measures of cellular immune function, especially changes in cellular immune function during stress (see Chapter 31 of this volume for a general review of psychometric issues).

Marsland and associates (1995) reported data on the three-week temporal stability of several quantitative and functional immune measures in response to a stressful speech task. The researchers found that most baseline quantitative measures of immunity (e.g., CD4+, CD8+ T-cells) evidenced significant temporal stability (0.22 ≤ r ≤ 0.75). Moreover, immune responses to acute stress were also associated with significant temporal stability for most quantitative measures (0.25 ≤ r ≤ 0.53), as well as changes in the proliferative response of PBLs to PHA (r = 0.50, p < 0.005).

Two separate studies of males and females (Mills, Haeri, & Dimsdale 1995a; Mills et al. 1995b) reported significant six-week test–retest scores for baseline quantitative measures of CD4+ T-cells (r = 0.57, 0.61), CD8+ T-cells (r = 0.70, 0.50), and CD4+/CD8+ cell ratio (r = 0.92, 0.90). Residualized change scores for NK cells (i.e. CD56+) and the CD4+/CD8+ ratio of T-cells (r = 0.55, 0.60) in response to acute stress also evidenced significant temporal reliability. In contrast to Marsland and colleagues, the test–retest correlation for CD8+ cells in response to acute stress was not significant in either study; this may reflect the longer test–retest interval utilized by Mills and colleagues.

Llabre and colleagues (1991) discussed the conditions under which simple change scores or residuated change scores might contain more measurement error. In general, the measurement reliability of these change scores depends, in part, on rXY (i.e., the correlation between pre-task and task values) and SDX/SDY. When rXY > SDX/SDY, there is more measurement error inherent in residuated change scores than simple change scores (Llabre et al. 1991; Zimmerman & Williams 1982a,b). However, prior research emphasizing the poor reliability of simple change scores (e.g., Chronbach & Furby 1970) has assumed equal variances in x and y (i.e., SDx/SDy = 1). Under such conditions, residuated change scores typically provide greater reliability, since the upper bound of a correlation is 1. In most psychophysiological studies, SDx/SDy is typically less than 1 because task values usually contain more variability than baseline values; the same appears to be true of laboratory PNI reactivity studies (Cacioppo et al. 1995). Thus, in practice, simple change scores appear to produce reliability levels that are equal to residualized change scores (Kasprowicz et al. 1990). Because of the lack of studies comparing these indices of changes in PNI studies, it would be helpful for future research to report data on both simple change and residualized change scores.

According to psychometric theory, several assessments of an individual across times and situations are likely to provide a more accurate individual difference assessment of immune function. Consistent with this possibility, Fletcher and associates (1997) found that the proliferative responses of PBLs to PHA, pokeweed mitogen, and NK cell activity were characterized by adequate generalizability coefficients (G > 0.70), which increased when assessments were aggregated across times (G ≥ 0.85). Unfortunately, the high costs of immunological assays make repeated determinations difficult in many circumstances. Although the data reviewed here suggest that measures of immune response are characterized by adequate-to-good temporal reliability, additional data are needed to examine an individual difference assessment of immune function.

**Unanswered Questions and Future Directions**

We have attempted to cover the important physical, social, and inferential elements involved in PNI research. As evidenced by this chapter, progress in PNI research has been
rapid as advances in areas such as psychology, endocrinology, neuroscience, and immunology have fueled continued growth. However, there are important questions that warrant increased attention in future research.

Perhaps the most common criticism of human PNI research is the question of health consequences of psychosocially mediated immune changes (Borysenko 1987; Cohen & Herbert 1996; Kemeny et al. 1992). There is a growing body of evidence suggesting that such immune alterations may have an influence on diseases such as cancer and infectious illnesses (Cohen et al. 1991; Kiecolt-Glaser et al. 1992; Kiecolt-Glaser et al. 1996; see also Kiecolt-Glaser & Glaser 1995) as well as wound healing (Kiecolt-Glaser et al. 1995; Manucka, Kiecolt-Glaser, & Faveghi 1997). Future research is needed, however, to more firmly establish this critical link, and well-designed prospective studies will be helpful in providing more definitive data on this issue.

There are significant questions raised by the basic research on neuroendocrine-immune interactions. In some cases, discrepancies are apparent in comparing in vitro and in vivo data. In vitro data, much like tightly controlled laboratory studies, allow for the isolation of direct influences of hormones on immune function. However, such data may be a simplistic model of neuroendocrine-immune interactions in vivo, where multiple mediating processes may be involved. An examination of both models will provide for a more complete understanding of neuroendocrine-immune interactions.

It is also clear that where immune cells are sampled may contribute significant variance. For instance, different patterns appear for some neuroendocrine-immune interactions when lymphocytes are sampled from peripheral blood or the spleen (Cunnick et al. 1992; Fechko et al. 1993; Lyle et al. 1993). For instance, Cunnick et al. (1992) found that foot shock in rats resulted in decreased Con A response of leukocytes in both blood and spleen. However, the mechanisms or antecedent processes were different for blood and splenic Con A reductions. The decreased blood proliferative response of cells to Con A was reduced in adrenalectomized rats, suggesting mediation via corticosterone. In comparison, the decreased splenic Con A response appeared mediated by catecholamines, since β-adrenergic antagonists reduced this effect. These reported differences may be attributable to (a) differing proportion of specific immune cells in compartments that may have different sensitivity to selected hormones or (b) greater hormonal release in specific compartments of immunity.

The temporal reliability of common measures of immunity warrants future inquiry. The few studies that exist suggest that many quantitative and some functional measures of resting and stress-induced immune change may be temporally stable. Increasing the reliability of immune measures presents a significant challenge given that repeated measurement— which would enable greater reliability through aggregation—is often prohibitive owing to the high cost of many immune assays. The simultaneous collection of such data in larger-scale prospective studies may prove valuable in examining this issue.

Research on cardiovascular reactivity to acute psychological stress has revealed important psychosocial moderators of cardiovascular reactivity such as coping responses (Gerin et al. 1992b; Sherwood, Dolan, & Light 1990), trait hostility (Christensen & Smith 1993; Lepore 1995), and social support (Gerin et al. 1992a; Kamarck, Manuck, & Jennings 1990; Lepore, Allen, & Evans 1993; Uchino & Garvey 1997). These data are, by and large, lacking in human PNI research. Future studies are needed to examine conceptually relevant psychosocial moderators of stress-induced immune changes, since these data may have important implications for interventions aimed at altering immunity in at-risk populations.

NOTES

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1. The following section on the history of immunity is summarized from the historical perspective of Silverstein (1989). Readers interested in a more detailed overview are referred to this very readable account of the history of immunology.

2. We should note that there is considerable controversy regarding suppressor cells. For instance, it is unknown whether such cells are a distinct subset of lymphocytes or rather cytotoxic T-cells that serve dual roles (Abbas et al. 1994).

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