Principles of psychophysiology
Physical, social, and inferential elements

Edited by

JOHN T. CACIOPOPO
The Ohio State University

and

LOUIS G. TASSINARY
University of Iowa

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6 Psychoneuroimmunology

SUSAN KENNEDY, RONALD GLASER, AND JANICE KIECOLT-GLASER

6.1 INTRODUCTION

During the last several years, empirical evidence has begun to accumulate supporting the notion that psychological factors may significantly affect the body's ability to combat or succumb to infection or disease. Moreover, the complex interactions between the immune, nervous, and endocrine systems are just now being realized. Although still in its infancy, psychoneuroimmunology has begun to unravel some of these intricate interactions and has led to a clearer understanding of the ways in which they operate.

As its name suggests, psychoneuroimmunology is a multidisciplinary science and, as such, is both unique and important, enabling the amalgamation of several seemingly diverse, yet intimately linked areas of study.

This chapter will attempt to provide an overview of some recent developments in the field of human psychoneuroimmunology. Beginning with a summary of the major cells of the human immune system and their functions, a general examination of neuroendocrine-immune interactions will be presented; finally, data implicating psychological and psychosocial factors in immunomodulation will be discussed.

Although this chapter focuses on human psychoneuroimmunology, the reader should be aware of the rather extensive animal literature (e.g., Borysenko & Borysenko, 1982; Justice, 1985) and should consult this literature for any questions or interest that may arise in this regard while reading this review.

6.2 THE HUMAN IMMUNE SYSTEM: BASIC ELEMENTS AND MECHANISMS

The human immune system is comprised of a variety of different cell types, each having its own function, yet all highly interrelated and orchestrated with each other. Although an in-depth view of the immune system is beyond the scope of this chapter, a general overview will be presented that will serve as the basis for understanding many concepts and empirical findings that follow.

Classically, the immune system has been functionally divided into two general categories: nonspecific responses and specific responses (see Roitt, Brostoff, & Male, 1985). Nonspecific responses refer to the general bodily defenses that follow initial contact with a pathogen and include the activation of phagocytic cells that engulf and destroy the invading agent as well as the activation of Natural Killer (NK) Cells, which continually monitor the body for infectious agents. If these nonspecific responses fail to prevent infection, more specific immune responses are activated. These responses include those mediated by lymphocytes, namely, antibody
Table 6.1. *Major cells of the human immune system*

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Origin</th>
<th>Primary functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Helper/inducer T-lymphocytes</td>
<td>Thymus</td>
<td>Initiation of immune response; replicates upon contact with antigen; releases lymphokines that stimulate T-cell replication; activates antibody production by B-lymphocytes</td>
</tr>
<tr>
<td>2. Suppressor/cytotoxic T-lymphocytes</td>
<td>Thymus</td>
<td>Inhibition of immune responses, primarily by suppressive effects on B-cell antibody production</td>
</tr>
<tr>
<td>3. B-lymphocytes</td>
<td>Bone marrow (?)</td>
<td>Production of antibody that binds to antigen</td>
</tr>
<tr>
<td>4. Natural Killer Cells</td>
<td>?</td>
<td>Surveillance and destruction of virally infected and tumor cells; activated by interferon</td>
</tr>
<tr>
<td>5. Macrophages</td>
<td>Bone marrow</td>
<td>Phagocytosis and destruction of foreign substances; produce IL-1 that stimulates T-helper lymphocytes; presents antigens to T-lymphocytes</td>
</tr>
</tbody>
</table>

production by B-lymphocytes (referred to as humoral immunity) as well as responses mediated by T-lymphocytes (cellular immunity).

An important distinction between the two types of immune responses is that lymphocyte-mediated responses may involve "immunological memory." That is, initial contact with a pathogen may induce a memory for that pathogen, such that reexposure results in a less severe disease or no disease at all.

A more detailed description of the cells of the immune system and their functions follows; Table 6.1 summarizes each cell type, its origin, and function.

6.2.1 *Lymphocytes*

Lymphocytes constitute those cells of the immune system that originate in the thymus (thymus derived; T-lymphocytes). They also include mononuclear cells of the avian bursa of Fabricius (B-lymphocytes). Although the human equivalent of the bursa is unknown, one postulated site is the bone marrow. T-lymphocytes manufacture several important chemical substances that serve to initiate immune responses following initial contact with a foreign substance (antigens, pathogens, and other substances that elicit antibody formation). In addition, T-lymphocytes help activate the production of antibody from B-lymphocytes.

T-lymphocytes are further subdivided on the basis of their function. T-helper/inducer cells, for example, are critical for the immune response, in that they assist in the production of antibody by B-lymphocytes. Helper/inducer cells also produce several important substances called lymphokines, each with diverse, yet crucial immunoenhancing properties. One such lymphokine is interleukin-2, a protein that promotes the replication of T-helper cells (and is sometimes referred to as T-cell
growth factor), as well as T-lymphocytes destined to become killer cells (cytolytic T-lymphocytes). Gamma-interferon is a glycoprotein released from T-helper/inducer cells following initial contact with a virus or antigen. Its primary functions include increasing the lytic ability of tumor-destroying cells (NK cells) as well as the protection of cells from virus infection.

In addition to helper cells, one subclass of T-lymphocytes has the role of inhibiting or down regulating the immune response, primarily by effects on T-helper cells. These cells, termed T-suppressor/cytotoxic cells, inhibit B-lymphocytes primarily by the inhibition of antibody production.

It is possible to experimentally quantify the percentages of various kinds of blood cells by the use of commercially available monoclonal antibodies. Monoclonal antibodies are produced by the fusion of antigen-primed spleen cells and myeloma cells and are used for the identification of certain "markers" on the cell surface. For example, the CD4 marker identifies helper/inducer lymphocytes; CD8 identifies suppressor/cytotoxic cells.

In addition to quantification methods, T-lymphocytes are also widely studied from a functional perspective through the use of mitogens, substances that can induce lymphocyte proliferation. Mitogens are thought to represent a valid in vitro model of how cells might respond to antigens that are encountered naturally. The most commonly used mitogens include concanavalin A (Con A) and phytohemagglutinin (PHA), which can stimulate T-lymphocytes, and pokeweed mitogen (PWM), which can stimulate B-lymphocytes.

In contrast to T-cells, B-lymphocytes mature into plasma cells, whose primary function is the synthesis and secretion of antibody molecules that bind to specific antigens. In addition, B-cells are characterized by the presence of surface immunoglobulin (Ig), which can be detected by the use of fluorescent antibodies. In one widely used immunological assay, indirect immunofluorescence, for example, serum or plasma to be tested is absorbed to antigen-producing cells. Antibody present in the serum will bind to a given specific antigen; identification and quantification of the antibody is revealed after absorption with a fluorescent antibody complex to an immunoglobulin (e.g., to the IgG, IgA, or IgM). In this way, antibody levels (titers) in serum or plasma can be assessed.

6.2.2 Natural Killer Cells

Natural Killer Cells (NK cells) are cells whose primary function appears to be the surveillance and destruction of certain tumor cells and virally infected cells; they are believed to have a role in tumor surveillance. The lytic capacity of NK cells is significantly enhanced by gamma-interferon, primarily by the development of mature NK cells from progenitors; furthermore, NK cells are believed to produce interferon. In order to experimentally study the lytic ability of NK cells, peripheral blood lymphocytes are typically incubated with "target" cells (e.g., tumor cells) that are made radioactive using a label (e.g., 51Cr). Following incubation, cell supernatants are harvested, and the percentage of lysis of targets from cells is determined by the amount of radioactivity released from the lysed cells.

6.2.3 Macrophages

Macrophages are large, nonlymphoid cells whose primary function is the ingestion and degradation of foreign matter. In addition, macrophages may also present
antigens to T-helper cells and may thereby initiate the cascade of events involved in the immune response (i.e., T-cell replication and lymphokine production, antibody stimulation from B-cells, etc.). This latter function appears to be related to the release of a chemical, interleukin-1 (IL-1), which upon release stimulates T-cells and triggers their replication.

6.3 NEUROENDOCRINE–IMMUNE INTERACTIONS

The cells of the immune system are now recognized as interacting not only with one another, but also with the nervous and endocrine systems. This complex neuroendocrine–immune network has prompted several investigations into the mechanisms that govern such interactions and has led to a clearer understanding of the ways in which these systems may communicate. Some of these possible communicative channels will be described in what follows, including the immune system’s interaction with the hypothalamic–pituitary axis, the existence of receptors on lymphoid tissue, and neurotransmitter innervation of certain lymphoid organs.

One of the primary mechanisms by which the nervous system interacts with the immune system is by the release of neurohormones, such as ACTH (adrenal corticotrophic hormone) from the pituitary.

Specifically, the hypothalamus, via corticotrophic releasing factor (CRF), triggers the release of pituitary ACTH, which subsequently signals the release of cortisol and other corticosteroid hormones from the adenal cortex. Levels of ACTH have been found to be sensitive to a variety of immune challenges, including psychological stress (e.g., Hennessy & Levine, 1979; Rose, 1980). Moreover, increased cortisol levels have been reported following prolonged strenuous physical activity as well as during biopsy and during or prior to surgery (see Rose, 1980, for a critical review).

Recently, Blalock and his colleagues (Blalock, Harbour–McMenamin, & Smith, 1985) have modified the “classic” concept of the hypothalamic–pituitary axis to include immune mechanisms. This modification is based primarily on the finding that ACTH is manufactured by lymphocytes and has immunosuppressive effects via the inhibition of gamma–interferon production by T-helper lymphocytes (Johnson, Torres, Smith, Dion, & Blalock, 1984). Blalock et al. (1985) have speculated that when the immune system encounters a viral agent or other antigen, hypothalamic CRF signals lymphocytes to produce ACTH. In this way, neural signaling by the hypothalamus is thought to represent one mechanism of communication with the neuroendocrine and immune systems.

In addition to interactions with the neuroendocrine system, lymphocytes have recently been found to express surface receptors for several neuroendocrine and neurotransmitter substances (Blalock, Bost, & Smith, 1985; O’Dorisio, Wood, & O’Dorisio, 1985; Pert, Ruff, Weber, & Herkenham, 1985; Russell et al., 1985; Wybran, Appelboom, Famaey, & Govaerts, 1979). For example, cholinergic receptors have been identified on lymphocytes (Lopker, Abood, Hess, & Lionetti, 1980). In addition, lymphocytes possess surface receptors for several neuropeptides, including vasoactive intestinal peptide (VIP) and somatostatin (Bhathena, Schecter, Gazdan, Louie, & Recant, 1980; O’Dorisio et al., 1985; Pert et al., 1985; Recant, Voyles, Luciano, & Pert, 1981).
The opiate peptides (enkephalins, endorphins) have been targeted by investigators because of their influence on the immune system. In addition to their widespread distribution in both the central nervous system and the periphery, lymphocytes appear not only to bear receptors for these neuropeptides, but also to produce substances similar to β-endorphin following certain viral infections (Smith & Blalock, 1981).

Functionally, the endorphins have been studied with respect to their effects on mitogen-stimulated lymphocytes and on the activity of NK cells. McCain and his colleagues (McCain, Lamster, & Bilotta, 1986), for example, have reported an inhibition of blastogenesis when β-endorphin was added to cultures containing phytohemagglutinin. However, since the inhibition was not blocked by the opiate antagonist naloxone, the authors concluded that the effects of β-endorphin were probably mediated by a nonopiate receptor. Other studies, however, have reported opposite effects. Thus, Weber and Pert (1984) have found enhancing effects of β-endorphin on lymphocyte proliferation to PHA as well as on the production of IL-2 from a mouse-derived T-cell line. Both of these effects were reversed by naloxone. Similarly, Plotnikoff and Miller (1983) reported enhanced blastogenesis with PHA with both leu-and met-enkephalin.

The ability of NK cells to lyse targets is also affected by opiates. Lysis has been found to increase significantly when β-endorphin is added to cultures of human lymphocytes and target cells (Kay, Allen, & Morley, 1984; Mathews, Froelich, Sibbit, & Bankhurst, 1983); similar results are obtained with met-enkephalin (Mathews et al., 1983).

Quite recently, Pert and her colleagues (1985) have demonstrated that human monocytes (progenitors of macrophages) will chemotax toward opiates. That is, monocytes will migrate toward opiates (as well as toward other neuropeptides) when placed in an experimental chamber. Importantly, chemotaxis is blocked when the specific antagonist to the neuropeptide is added. Pert et al. suggest that the existence of opiate receptors on immune cells may represent a communication medium between the central nervous system and the immune system.

Finally, the nervous and immune systems may communicate by way of direct neurotransmitter innervation of lymphoid tissue. For example, immune tissue receives input from the sympathetic autonomic nervous system (Besedovsky, del Rey, Sorkin, Da Prada, & Keller, 1979), as evidenced by altered immune responses following pharmacologic manipulation of the innervating fibres. In a recent report, Felten and his colleagues (Felten, Felten, Carlson, Olschowka, & Livnat, 1985) have demonstrated noradrenergic nerve terminals on several lymphoid structures, including the thymus, bone marrow, and spleen. Terminal endings were located close to lymphocytes and macrophages as well as other cell types. Felten et al. suggest that the presence of noradrenergic nerve terminals may serve to communicate with receptors located on adjacent cells (e.g., on lymphocytes).

In addition to noradrenergic innervation, lymphoid tissue may be innervated by neuropeptides, including VIP and met-enkephalin (Felten et al., 1985). Such innervation may serve as a communicative link with neuropeptide receptors on the surface of lymphocytes and demonstrates another potential mechanism by which the nervous, endocrine, and immune systems are intricately orchestrated.

Given these mechanisms, it now becomes important to examine the ways in which psychological stressors may influence immune function.
6.4 Psychological and Psychosocial Factors and Immunity: Links Between Stress and Health

The notion that psychological stress may increase an individual's susceptibility to infection or disease has, until quite recently, been highly speculative. Over the last several years, however, an impressive amount of empirical data has begun to accumulate suggesting the link between psychological/psychosocial factors and immune competence.

6.4.1 Major life events and immune function

In an early study of the effects of psychological stress on immunity, Bartrop and his colleagues (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977) examined lymphocyte function in bereaved individuals subsequent to the death of a spouse. Relative to controls, lymphocytes from the bereaved subjects showed depressed responses to the mitogens Con A and PHA 6 weeks following the spouse's death. Because these changes occurred despite no differences in T-cell or B-cell number, immunoglobulins, or serum concentrations of several hormones, they are presumed to reflect functional alterations in lymphocytes rather than quantitative changes.

Using a prospective design, Schliefer and his associates (Schliefer, Keller, Camerino, Thornton, & Stein, 1983) investigated lymphocyte responses to mitogens in bereaved men both prior to and following the death of their wives from advanced breast cancer. Depressed responses to Con A, PHA, and PWM were found following the loss of the spouse relative to prebereavement levels. Because the same subjects were studied both during baseline and postbereavement, the depression in cell function is assumed to reflect the psychological stress associated with spousal death rather than an already existing depression resulting from the stress of terminal illness of a loved one. Importantly, as the authors note, stress associated with the spouse's terminal illness did not result in recovery of normal lymphocyte function (i.e., habituation) prior to the death of the spouse, indicating that the observed immune responses were a direct consequence of the stressful event.

One important question regarding stress-related immune changes involves the extent to which individuals may adapt to more chronic stressors in their environments; that is, when confronted with a stressor over relatively long time periods, does the immune system adapt and subsequently resume "more normal" levels of function? In order to assess this possibility, Kiecolt-Glaser and her colleagues (1987) have examined immune function in recently divorced or separated women. Marital satisfaction has been shown to be one of the most important contributors to an individual's overall happiness and psychological well-being (Glenn & Weaver, 1981); indeed, increases in illness and medical problems as well as increased mortality from infectious disease are reliably reported following the disruption of a marriage (Lynch, 1977; Somers, 1979; Verbrugge, 1979).

Kiecolt-Glaser et al. (1987) analyzed responses from separated or divorced (S/D) women and married controls on several psychological inventories, including the Brief Symptom Inventory (BSI; Derogatis & Spence, 1982), the UCLA Loneliness Scale (Russell, Peplau, & Cutrona, 1980), Kitson's attachment scale (Kitson, 1982), and the Dyadic Adjustment Scale (Spanier, 1976), an index of marital quality. Lymphocyte function and numbers were assessed using several immunological assays. Separated or divorced women who had been more recently separated
Table 6.2. *Mean* for 16 women who were separated 1 year or less and 16 matched married controls

<table>
<thead>
<tr>
<th></th>
<th>Separated-divorced women</th>
<th>Married women</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV VCA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>520.50 (706.84)</td>
<td>147.12 (191.88)</td>
</tr>
<tr>
<td>Percentage of helper T-lymphocytes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26.43 (7.59)</td>
<td>32.91 (7.03)</td>
</tr>
<tr>
<td>Percentage of suppressor T-lymphocytes</td>
<td>20.01 (6.70)</td>
<td>22.66 (7.76)</td>
</tr>
<tr>
<td>Helper-suppressor ratio</td>
<td>1.49 (0.66)</td>
<td>1.69 (1.47)</td>
</tr>
<tr>
<td>Percentage of NK cells&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.50 (5.05)</td>
<td>12.79 (8.05)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Plus or minus standard deviation, in parentheses.

<sup>b</sup> *p* < 0.05


(within 1 year of testing) were found to have significantly poorer immune function than married controls; specifically, lymphocytes from the S/D women showed poorer blastogenic responses to the mitogens Con A and PHA, indicating a deficit in the potential of cells to respond to naturally occurring antigens. Moreover, as shown in Table 6.2, separated women had significantly lower percentages of T-helper lymphocytes as well as lower percentages of NK cells. In addition, S/D women were found to have higher antibody titers to the Epstein–Barr Virus (EBV) virus capsid antigen (VCA), a human herpes virus that causes infectious mononucleosis. Elevated antibody titers to EBV are found in individuals undergoing chemotherapy as well as in persons with certain immunosuppressive disorders and are thought to reflect poorer cellular immune competence in holding the virus in check.

These data are in accord with epidemiological studies linking marital disruption to increased health risks (Verbrugge, 1979). It is noteworthy that the degree of attachment to the (ex)husband was found to be a significant indicator of psychological state, as well as immune function, with greater attachment predicting greater depression and compromised immune function. Previous studies have also pointed to the importance of healthy interpersonal relationships for both psychological and immunological well-being (e.g., Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Kiecolt-Glaser et al., 1984a, b) and suggest that such relationships may have health-related consequences.

In a follow-up study (Kiecolt-Glaser et al., 1988), S/D men and married controls were studied on several psychological and immunological measures. Separated or divorced men were found to have significantly higher antibody titers to EBV VCA as well as higher titers to herpes simplex virus. Moreover, S/D men were significantly more depressed than their matched controls and reported significantly more illness in the 2 months preceding the test session.

In a related study assessing chronic stressors and immune function, family caregivers of victims of Alzheimer's disease were studied (Kiecolt-Glaser et al., 1987). Alzheimer's disease is an irreversible degenerative disease of the central
nervous system characterized in later stages by severe memory loss, incontinence, and an inability to care for oneself (Heckler, 1985; Reisberg, 1983). Because the time course of the disease is lengthy, with a modal survival time of 8 years after onset, caregiving by family members may well be considered a chronic stressor. Caring for a victim of Alzheimer's has been reported to be associated with clinical depression (Eisdorfer, Kennedy, Wisnieski, & Cohen, 1983); in addition, self-report data from caregivers has suggested that as the afflicted family member becomes progressively more impaired, there is a corresponding decrease in life satisfaction on the part of the caregiver as well as increases in their psychiatric symptoms (George & Gwyther, 1984).

In our study, psychological and immunological data from 34 caregivers and 34 sociodemographically matched control subjects were assessed. Caregiving time in the study ranged from 9 months to 16 years, with mean caregiving time of 5.45 years. Consistent with previous studies (Eisdorfer et al., 1983; George & Gwyther, 1984), caregivers reported greater psychological distress and greater loneliness than controls; in addition, caregivers had significantly lower percentages of total lymphocytes, lower percentages of T-helper cells, and higher antibody titers to EBV VCA.

Collectively, these data suggest that there is not measurable immunological or psychological adaptation to the level of well-matched comparison subjects to two long-term stressors. An important question that arises when one considers the existing literature on chronic stressors and immune competence is whether such stressors are associated with changes in health status (e.g., frequency of illness throughout the course of a divorce,). Unfortunately, there are no data at present that are sufficient to answer this question. What is clearly needed in the area of human psychoneuroimmunology are studies aimed at following the same individuals over long periods of time, with psychological and immunological assessments made at various points. In addition, these studies must include medical examinations and neuroendocrine assessments in order to provide a complete health profile on the individuals being studied.

In the two sections that follow, data will be presented suggesting that more short-term, acute stressors may also have adverse effects on T-lymphocyte function as well as on the ability of NK cells to monitor that body for potentially carcinogenic cells.

6.4.2 Stress and cancer

Carcinogens are present in various forms in the environment. For example, many foods, such as meat, are processed with nitrates, and pesticide residues exist on fresh fruits and vegetables. Sunlight emits potentially harmful radiation while industrial by-products provide carcinogenic chemicals to the air (Miller, 1978). Although ubiquitous, however, exposure to carcinogens is usually limited or at levels below that which is cancer producing.

The mechanism by which carcinogenic agents produce cancer is believed to be via damage to cellular DNA. Once altered, the DNA may either undergo repair or remain impaired, thereby producing a mutant (cancerous) cell that subsequently proliferates (Setlow, 1978). Once transformed, the mutant cells may be destroyed by immune surveillance, for example, by NK cells (Herberman, 1982; Herberman et al., 1982). Hence, the body may respond to carcinogen exposure both by activation of an
intracellular repair process and by the surveillance and destruction of tumors by NK cells.

To examine a possible direct relationship between psychological stress and carcinogenesis, 28 newly admitted, nonpsychotic, nonmedicated psychiatric patients were divided into high- and how-distress subgroups based on their responses to the Depression Scale of the MMPI (Minnesota Multiphasic Personality Inventory; Kiecolt-Glaser, Stephens, Lipetz, Speicher, & Glaser, 1985). Lymphocytes from both groups were exposed to X-irradiation in order to damage cellular DNA. High distress was found to be associated with poorer DNA repair, whereas better DNA repair was associated with low distress. These stress-related deficits in DNA repair may have critical implications in terms of the etiology of cancer cells. In addition, when lymphocytes are confronted with an antigen, they typically respond by increases in cellular DNA and subsequent proliferation. These responses aid in attacking the foreign invader and thereby in warding off disease. Impairments in DNA may therefore limit the cell's ability to divide and combat infection.

In a similar vein, it has been found that psychiatric patients may be more susceptible to cancer (Ernster, Sacks, Selvin, & Petrakis, 1979; Fox, 1979) and that high MMPI depression scores are associated with a higher incidence of cancer (Shekelle et al., 1981).

As previously mentioned, impaired cellular DNA may result in the transformation of cells to a mutant state, which may involve subsequent destruction by NK cells. Recent data suggest that the ability of NK cells to destroy tumors may be adversely affected by psychological stress (Aarstad, Gaundernack, & Seljeld, 1983; Herberman, 1982; Kiecolt-Glaser et al., 1984a,b; 1986; Shavit, Lewis, Terman, Gale, & Liebeskind, 1984). In one such study, for example (Locke, Kraus, & Leserman, 1984), college students reporting limited psychological distress despite high levels of life change stress had higher NK cell activity than students reporting high psychological stress. More recently, Glaser and his colleagues (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986) examined NK activity and total NK in second-year medical students during final examinations as well as 6 weeks before exams. As shown in Figure 6.1, NK cell lysis significantly decreased during examinations relative to baseline at all effector-to-target-cell ratios. In addition to the impaired NK lysis, the percentage of NK cells (as determined by using a monoclonal antibody) decreased during examinations. Concomitant with deficits in NK cell number and activity, interferon levels produced by mitogen-stimulated lymphocytes were also found to decrease significantly during examinations (Table 6.3). Interferons are glycoproteins that are produced by cells upon viral infection or antigenic or mitogenic stimulation. Upon release from a stimulated cell, interferon binds to surface receptors on adjacent cells, thereby triggering the synthesis of proteins aimed at destroying the virus. One well-documented function of interferon is its enhancement of NK cell lysis (e.g., Herberman et al., 1982) by activation of NK precursors into a lytic state. Stress-associated decreases in interferon levels, therefore, may clearly have adverse consequences for immune competence via effects on NK cells.

Self-report data confirmed that examinations were more stressful as compared to baseline. These data imply that relatively commonplace stressful events may have serious effects for immune function. Stress-induced deficits in NK cells may ultimately result in poorer surveillance and destruction of transformed cells. Collectively, the data suggest that psychological stress and its concomitant alterations in cellular immunity may increase the susceptibility of individuals to
Figure 6.1. Means (plus or minus SEM) for percent lysis of MOLT-4 cells for three NK effector-to-target-cell ratios at baseline and during examinations. (Copyright 1986 by the American Psychological Association. Reprinted by permission of the publisher and author.)

Table 6.3. Mean\(^a\) of IFNs produced by PBLs stimulated with Con A and plasma IFN levels at baseline and during examinations

<table>
<thead>
<tr>
<th>Sample</th>
<th>Leukocyte IFNs (U/ml)</th>
<th>Plasma IFNs (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(M)</td>
<td>2,003.03</td>
<td>0</td>
</tr>
<tr>
<td>(SE)</td>
<td>179.13</td>
<td>0(\text{'})</td>
</tr>
<tr>
<td>Examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(M)</td>
<td>80.00</td>
<td>0</td>
</tr>
<tr>
<td>(SE)</td>
<td>17.99</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Plus or minus standard error (SE); \(M\), mean.

*Note:* Abbreviations: IFN, interferon; PBL, peripheral blood leukocytes. Reprinted by permission of the publisher and author. Copyright 1986 by the American Psychological Association.

Infection or to malignant disease either via faulty repair of cellular DNA or by impairments in NK cells to monitor and destroy mutant cells.

6.4.3 Minor life events and immunity

In the preceding section on psychological factors and immunity, recent findings were documented that support the link between major stressful life events and suppressed immune function. Fortunately, such major life events are generally not encountered with any regularity throughout the course of one’s lifetime; rather, smaller scale “minor” stressors are far more common. Given the frequency with
which minor stressors are encountered, it is important to examine their influence on the immune system and on health.

For the last several years, our laboratory has been involved in the study of one commonplace stressor, academic examinations and their impact on immune function (e.g., Glaser et al., 1986; Kiecolt-Glaser et al., 1986). Medical students at Ohio State take examinations concurrently as a group, making for ideal experimental conditions.

Psychological and immunological data are obtained from 30 first-year medical students at six sample points over the course of the academic year. The first, third, and fifth of these samples occur approximately 1 month prior to exams (baseline), whereas the second, fourth, and sixth occur during examinations (stress). Such a design enables data from the same students to be compared in pairs (i.e., in three sets of baseline–stress dyads) over relatively long periods of time (one academic year).

In addition to the aforementioned deficits in NK cell activity associated with examinations (see section 4.2), several other indices of immunosuppression have reliably been documented in our medical student population during exams. For example, lymphocyte responses to two mitogens (Con A and PHA) are consistently and significantly lower relative to baseline tests (Glaser et al., 1985; see Figure 6.2). Furthermore, percentages of T-helper and T-suppressor cells are often found to be lower during exams, which may indicate a functional deficit in these cell types. Importantly, although these changes are not associated with any major illnesses in the students, there are self-reported increases in upper respiratory tract infections during exams. Concomitant with these immune changes, responses on psychological inventories support the stressful nature of the exams.

These data are important, as they demonstrate that the immune system is sensitive to relatively minor life events and the psychological stress associated with these events may ultimately result in an immunocompromised state. Moreover, it is critical to keep in mind that medical students are quite adept at test taking and yet
are significantly immunosuppressed. Given a not-so-healthy population, however (e.g., the elderly), such minor life stressors and the psychological and immune changes associated with them might, in fact, result in increased incidence of overt physical illness, infectious disease, or cancer (Glaser et al., 1985).

6.5 CONCLUDING COMMENTS

Although a relatively new discipline, psychoneuroimmunology has already begun to shed light on the complex interactions between the nervous, endocrine, and immune systems. This multifaceted approach is long overdue and promises to increase our knowledge as to how these systems work together in health and in disease.

For example, the links between psychological distress and suppressed immune function are becoming well recognized. What remains to be learned, however, are the mechanisms that operate in individuals during long periods of stress: These mechanisms may include neuroendocrine changes, changes in lymphocyte receptor number or sensitivity, or alterations in lymphokine levels that have feedback consequences on levels of circulating neuroendocrines. Clearly, the need for such longitudinal studies is imperative to understand the effects of chronic stressors on immune function.

In addition to the need for longitudinal efforts, other important questions remain unanswered. These include how individual “coping” mechanisms are manifested in immune function, how neurotransmitters interact with lymphocytes and lymphokines in both acute and chronic stress, and how stress that is experienced early in development affects later immune function.

REFERENCES


