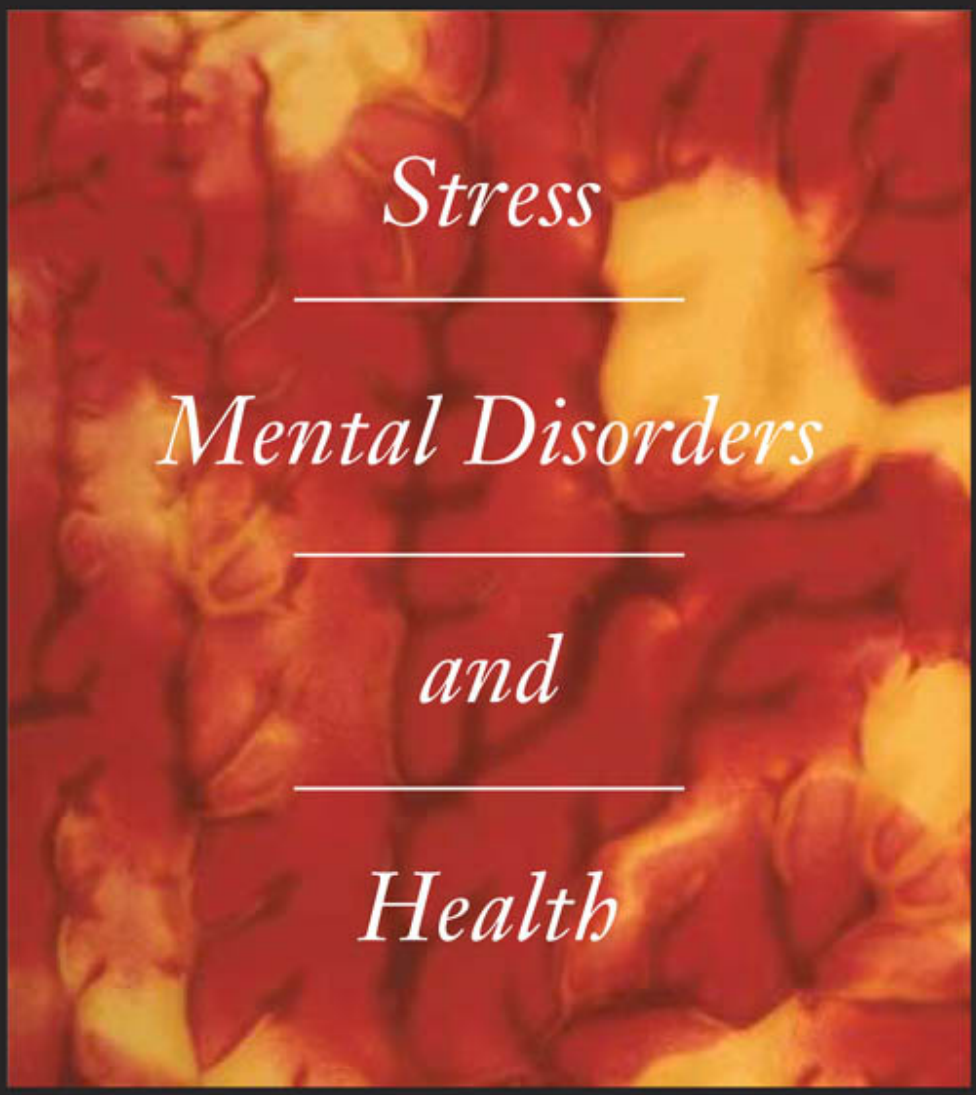
PSYCHONEUROIMMUNOLOGY



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Karl Goodkin, M.D., Ph.D.

Adriaan P. Visser, Ph.D.

Psychoneuroimmunology

Stress, Mental Disorders, and Health

PROGRESS IN PSYCHIATRY

DAVID SPIEGEL, M.D., SERIES EDITOR

Number 59

Psychoneuroimmunology

Stress, Mental Disorders, and Health

Edited by
Karl Goodkin, M.D., Ph.D.
Adriaan P. Visser, Ph.D.

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Introduction to the Progress in Psychiatry Series

The Progress in Psychiatry Series is designed to capture in print the excitement that comes from assembling a diverse group of experts from various locations to examine in detail the newest information about a developing aspect of psychiatry. This series emerged as a collaboration between the American Psychiatric Association's (APA) Scientific Program Committee and the American Psychiatric Press, Inc. Great interest is generated by a number of the symposia presented each year at the APA annual meeting, and we realized that much of the information presented there, carefully assembled by people who are deeply immersed in a given area, would unfortunately not appear together in print. The symposia sessions at the annual meetings provide an unusual opportunity for experts who otherwise might not meet on the same platform to share their diverse viewpoints for a period of 3 hours. Some new themes are repeatedly reinforced and gain credence, whereas in other instances disagreements emerge, enabling the audience and now the reader to reach informed decisions about new directions in the field. The Progress in Psychiatry Series allows us to publish and capture some of the best of the symposia and thus provide an in-depth treatment of specific areas that might not otherwise be presented in broader review formats.

Psychiatry is, by nature, an interface discipline, combining the study of mind and brain, of individual and social environments, of the humane and the scientific. Therefore, progress in the field is rarely linear—it often comes from unexpected sources. Furthermore, new developments emerge from an array of viewpoints that do not necessarily provide immediate agreement but rather expert examination of the issues. We intend to present innovative ideas and data that will enable the reader to participate in this process.

We believe the Progress in Psychiatry Series will provide you with an opportunity to review timely, new information in specific fields of interest as they are developing. We hope you find that the excitement of the presentations is captured in the written word and that this book proves to be informative and enjoyable reading.

David Spiegel, M.D.
Series Editor
Progress in Psychiatry Series

Introduction

The introduction to this book is a pleasure to write, since it represents the culmination of a great deal of international collaborative work, particularly between my coeditor, Adriaan P. Visser, Ph.D., at the Helen Dowling Institute for Biopsychosocial Medicine in Rotterdam, the Netherlands, and myself (and my collaborators) at the University of Miami School of Medicine. In addition, it represents quite a bit of work from each of the contributing chapter authors and their respective collaborators.

This book was originally conceived as an extension of a symposium on psychoneuroimmunology presented at the 146th Annual Meeting of the American Psychiatric Association in 1993. The symposium consisted of presentations in the areas of behavioral genetics, the relationship between stressors and immunity in a medically healthy population, and the effects of stressors on immune function in specific populations of patients—those with major depressive disorder, cancer, and HIV/AIDS.

In Chapter 1, an expansion of the symposium presentation, Steven E. Keller and his colleagues begin with a well-studied, psychiatric clinical focus in the field of psychoneuroimmunology: the impact of psychosocial factors on immunity in patients with major depressive disorder. They extend this work to a healthy population as well. In Chapter 2, John M. Petitto and colleagues provide the important scientific background for psychoneuroimmunology, reviewing the impact of gender-specific factors, diurnal variation, and behavioral genetics on immune function.

Based on my own symposium presentation of psychoneuroimmunologic factors involved in cervical cancer, Chapter 3, by Adriaan P. Visser, myself, and our Dutch colleagues, represents work that I had begun on the association of psychosocial factors with stage of cervical intraepithelial neoplasia (or "dysplasia") and

invasive cervical cancer. A study building on that work is currently being conducted in Rotterdam, Leiden, and the Hague in the Netherlands. In this chapter, recent data are presented from this ongoing study funded by the Dutch Cancer Society in which Dr. Visser and I are collaborating.

Finally, the symposium presentations by Gail Ironson and by me of work conducted at the University of Miami School of Medicine on the impact of behavioral interventions in HIV-1-seropositive and HIV-1-seronegative homosexual men are represented in this book. In Chapter 9, Dr. Ironson and colleagues address the psychosocial predictors of immunologic measures and disease course in HIV-1 infection and the effects of stress management on disease progression. In Chapter 10, my colleagues and I examine the psychoneuroimmunology of bereavement, specifically as it relates to a bereavement support group intervention for HIV-infected individuals.

When the work presented at this symposium was first offered for consideration for publication in the Progress in Psychiatry series, we decided that a considerable extension of the scope of the symposium was warranted. One of the aspects chosen for inclusion was the role of psychoneuroimmunology in carcinogenesis and established tumor progression. Given that this is a developing area in which specific tumors of interest have as yet received only relatively limited attention in reviews, we felt that the topic merited some priority for attention here. As a result, three chapters focusing on this area have been included. Chapter 3, as described earlier, examines psychoimmunoneurologic issues in cervical cancer. In Chapter 4, Gieta van der Pompe, of the Helen Dowling Institute for Biopsychosocial Medicine in Rotterdam, the Netherlands, focuses on the potential impact of behavioral interventions as a "neoadjuvant" treatment in the oncologic surgical setting—a novel issue. In this chapter, Dr. van der Pompe also extends the focus on tumor progression to breast cancer—perhaps the specific tumor most frequently studied from a psychoneuroimmunologic perspective. In Chapter 5, Sara Stein and David Spiegel provide a comprehensive review of the psychoneuroimmunologic and neuroendocrine effects on cancer progression, a subject of broad

clinical relevance. Areas covered include the impact of specific psychotropic medications (i.e., antidepressants, lithium, and neuroleptics), the effects of psychosocial milieu (life stressors, such as bereavement; social support) and the individual's response to that milieu (emotional expression, humor), psychopathology (specifically depression), and associated neuroendocrine responses related to immunologic effects relevant to clinical progression of disease. Drs. Stein and Spiegel extend the earlier and well-known work conducted by the Stanford University breast cancer research group to encompass psychophysiologic issues. The work reported in this chapter might well be a forerunner of major research developments soon to come on the integration of these domains—not only in breast cancer treatment but also in cancer treatment generally.

A second area in which the focus of the book was expanded is that of the role of psychoneuroimmunology in HIV infection and AIDS. The symposium presentations—and the chapters based on them (Chapters 9 and 10)—as described earlier, focused on the impact of behavioral interventions with homosexual men. Dr. Ironson focused on the psychological, immunologic, and clinical impact of a cognitive-behavioral stress management intervention and an aerobic exercise training program. My colleagues and I at the University of Miami School of Medicine focused on the impact of a research-derived, semistructured bereavement support group intervention technique on immunity. Since these presentations were based on the impact of intervention, background information from natural history studies of psychoneuroimmunologic factors in HIV/AIDS was of relevance. For this reason, the chapter by Daniel J. Feaster and colleagues was included (Chapter 6). In that chapter, groundwork is laid for the use of a bereavement support group intervention in which bereavement support group techniques are integrated with our conceptualization of the impact of the psychosocial milieu in the immune system (as represented in the Stressor-Support-Coping model developed by me and my colleagues at the University of Miami School of Medicine). However, relationships of psychosocial factors and the immune system can be especially complex in a disease in which the immune system it-

self is the target, such as HIV-1 infection. Hence, two additional chapters were included that addressed several of the methodologic issues involved with examining psychoneuroimmunology research questions in the setting of relevant changes known to occur with the progression of this disease. In the first of these chapters, Chapter 7, Frances L. Wilkie and I focus on the neuropsychological changes relevant to psychoneuroimmunology research in HIV/AIDS. In the other chapter, Chapter 8, Paul Shapshak (from the point of view of virology), Mahendra Kumar (from the point of view of neuroendocrinology), Mary Ann Fletcher (from the point of view of immunology), and I, along with our colleagues, broaden the focus to address relevant underlying pathophysiology of the disease in multiple areas. In this sense, it is hoped that the book exemplifies an intensive focus on the psychoneuroimmunology research questions applied to the example of one specific disease process. This level of detail is required for the satisfactory application of this area of research to immunologic changes in patients with other diseases and for determination of the clinical relevance of any such immunologic changes that might be related to psychosocial factors.

Psychoneuroimmunology is an area in which the very name poses its multidisciplinary challenge. Various fields of research—not only those of psychiatry and psychology but also those of neurology, neuroendocrinology, and immunology—must be integrated. In the concluding chapter (Chapter 11), Cobi J. Heijnen, a world-renowned immunologist working in this area, integrates the disciplines contributing to the field of psychoneuroimmunology in relation to another disease, juvenile rheumatoid arthritis. In so doing, Dr. Heijnen points to the future potential clinical applications awaiting further investigations in the field. These applications will likely extend beyond diseases related to decreased immunologic function—whether the origin of the antigen involved is external (e.g., an infectious pathogen) or internal (e.g., a tumor-specific antigen)—to a different set of immunologically mediated diseases reflecting an increased immunologic response. Examples of such diseases are allergy, in the case of an external antigen, and autoimmune disease, in the case of an internal antigen.

With this extension the full clinical promise of the field of psychoneuroimmunology may eventually be fulfilled.

We feel the need to acknowledge a number of others playing a role in bringing this book to fruition. In particular, my support staff at the University of Miami School of Medicine, Ms. Gladys Chayeb and Mr. Edward Diez, were indispensable in completing multiple tasks, including but not limited to numerous phone calls to authors, distribution of drafts and revisions of chapters, coordination of the production of tables and figures, obtaining releases for reproductions of published work, and proofing of the final document. In addition, the support staff of the Helen Dowling Institute for Biopsychosocial Medicine, specifically Ms. Cock Kuipers and Ms. Ria Uyterlinden, are to be thanked for reviewing chapter references for conformation to format and for conversion of the computer textfiles into documents that can be read and printed in European as well as American formats. Without the efforts of these two support staffs, the ongoing and frequent need for us to have many detailed intercontinental communication exchanges across numerous modes of contact would not have been met and this book would not have been possible.

Karl Goodkin, M.D., Ph.D.

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Chapter 1

Stress, Depression, Immunity, and Health

Steven E. Keller, Ph.D., Steven J. Schleifer, M.D., Jacqueline A. Bartlett, M.D., Samuel C. Shiflett, Ph.D., and Pranela Rameshwar, Ph.D.

In recent decades, psychoneuroimmunology has emerged as a distinct discipline, advancing our knowledge of the relationships among psychosocial factors, the central nervous system (CNS), the immune system, and disease. This growing body of work has suggested that psychological states, including exposure to stressors and the presence of depressive states, may influence health and disease by altering immunologic states (Glaser et al. 1987; Kiecolt-Glaser and Glaser 1994). In this chapter, we provide a brief overview of some of the better established relationships among stressors and depression, the immune system, and health. Figure 1–1 presents a simple model that illustrates some of the most important putative connections among the variables discussed.

As Solomon (1993) pointed out, the relationship between bodily and psychosocial well-being has been observed throughout history and across cultures. Considerable scientific as well as lay interest has recently propelled the mind-body paradigm into the limelight, to be either praised as a new explanatory model of health and disease or damned as an inappropriate legitimization of old wives' tales lacking any basis in science. An increasing amount of scientific research has connected psychological factors, including stress and mood dysfunctions, to a host of illnesses and to the body's ap-

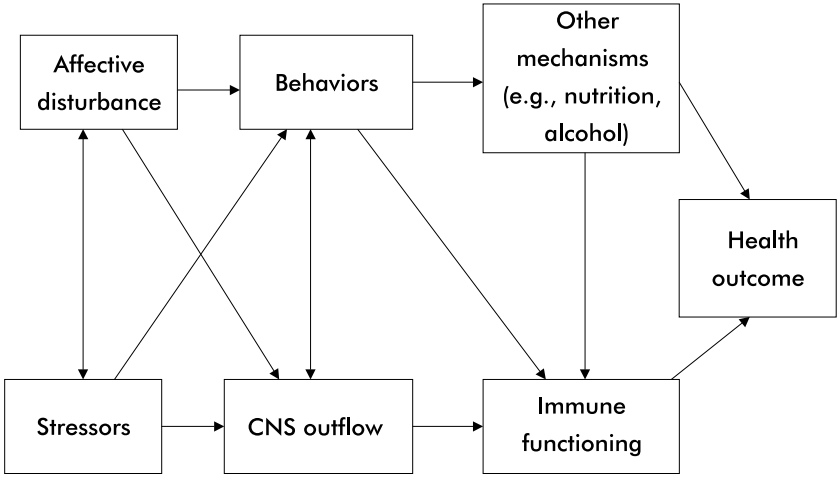

Figure 1–1. Relationships among life stressors and affective disturbances. Both life stressors and affective disturbances determine central nervous system (CNS) outflow and behavioral responses. Behaviors may affect immune functioning directly or through effects on other mechanisms. CNS outflow also directly affects immune functioning. Behaviors, associated mechanisms, and CNS outflow all have an impact on health outcomes.

parent ability to resist or overcome many life-threatening medical conditions (e.g., Everly 1989; Temoshok and Dreher 1993).

Because the immune system helps protect the body from infection, increased disease during periods of exposure to stressors has often been attributed to compromised immune function caused by cortically mediated stressor reactions. Indeed, a substantial body of evidence supports the idea that life stressors and clinical depression affect immune function. A weak link in this model, however, involves the difficulty in demonstrating a connection across the entire chain, from life stressors to immune function to clinical health outcomes. Observed changes in immune function in the presence of life stressors are often not obviously associated with changes in health, although this lack of association can readily be attributed in most cases to limitations in research methodology, especially limited power associated with sample size, small and temporary

changes in immune function, or selection of suboptimal immune or health markers (Keller et al. 1994). When rigorous research designs and sufficient statistical power are used, it is possible to demonstrate this connection (Cohen et al 1991; Kasl et al. 1979). A review of the limited number of studies in the research literature that present evidence for this connection has been provided by Keller and colleagues (1994).

Life Stressors and Depression

Life stressors and depression are among the psychosocial constructs that have been most extensively investigated in relation to immunity and health. They also merit attention as linked constructs that, when considered concurrently, may provide insight into a sequence of experiential and CNS effects of import to psychoneuroimmunology. The term *stress* has been used to apply to a wide range of environmental events that affect a person, as well as to the individual's reactions to a stressful life event. The term is often used to refer both to the stressor and to the entire process, including the stimulus (stressor) and the response (e.g., distress, coping response). Given the wide range of stressors and psychobiological stress reactions, early concepts that emphasized common aspects of stress processes (Selye 1976) must be applied with great caution in psychoneuroimmunology studies, as in other areas of investigation. Carefully differentiating among stressors, distinguishing stressors from stress reactions, and specifying the unique characteristics of specific stress responses are often essential to understanding reported stressor effects on immunity and health.

Recent reviews of the stress-immune association (Cohen and Williamson 1991; Herbert and Cohen 1993b; O'Leary 1990) have noted the many problems in accurately defining and measuring stress and have proposed differing taxonomies of stressors. A major problem in assessing stress reactions is that clinical and other observational judgments of distress do not always correspond to self-reports of distress. This lack of correspondence may be related

to factors ranging from precision of measurement to the presence of defense mechanisms (denial) that maintain an illusion of mental health (Shedler et al. 1993). Chronically distressed individuals may have altered immune systems yet appear to have normal functioning when functioning is assessed with most self-report–based measures, and unreported "distress" will weaken observed associations between stressors and immune function. Clinical judgments or highly objective assessments (e.g., of a specific life event) are therefore often preferable to assessments relying wholly on self-report or poorly validated instruments, although subjective reports may be important in some models.

The distinction between stressor and stress reaction works reasonably well in most contexts. However, a putative stress reaction may also serve as a stressor, such as in acute and chronic mood disturbances (e.g., major depressive disorder [Rigatelli et al. 1993]). Correspondingly, a "distress state" may be either linked to or presumably independent of a life stressor. For example, major depressive disorder often has no apparent precipitating external event, and other paradigmatic stress responses, such as grief reactions following bereavement, are often indistinguishable phenomenologically from major depressive disorder. In addition, reactive states such as posttraumatic stress disorder (PTSD) can occur in the context of a precipitating external event and include symptoms similar to those of major depressive disorder.

Life stressors and associated stress reactions may be inextricably intertwined. For example, the development of affective disturbances may be involved in the immune effects of stressors such as bereavement and separation. The affective changes and neurovegetative symptoms found in bereaved individuals often suggest the presence of a clinical affective disorder (Clayton et al. 1972; Osterweis et al. 1984; Parkes 1972), and depression, like bereavement, has been associated with increased prevalence of neoplastic and infectious diseases (Cappel et al. 1978; Odegaard 1952; Shekelle et al. 1981) and mortality (Avery and Winokur 1976; Murphy et al. 1987; Odegaard 1952; Shekelle et al. 1981).

Some studies have suggested that depression plays a major, if not essential, role in immune modulation following bereavement

(Evans et al. 1989; Weisse 1992). Linn and colleagues (1984) reported reduced lymphoproliferative responses to mitogen stimulation only in those bereaved subjects who had depressive symptoms, and Irwin and colleagues (1987) found a strong negative correlation between severity of depressive symptoms and both natural killer (NK) cell activity and CD8+ cell counts. Stein and colleagues (1991a, 1991b) have provided detailed reviews on depression, bereavement, and immune function. Weisse (1992) systematically examined the effects of bereavement and separation as they function to arouse depressive symptomatology as the intervening mood state between life stressor and immune function. She concluded that in bereaved subjects, indicators of immunocompetence are lower among people exhibiting depressive symptomatology and immune alterations may be more related to dysphoric mood than to specific situations or events.

It is important to note, however, that altered affective state (e.g., depression) may not be sufficient to induce immune change. Studies by our group and others have demonstrated a complex relationship between syndromal depressive disorder and the immune system (Stein et al. 1991a). For example, in our initial studies of major depressive disorder and immunity, we found significantly decreased in vitro lymphocyte proliferation in hospitalized patients with major depressive disorder compared with control subjects matched for age and sex (Schleifer et al. 1984). A second study of ambulatory patients with major depressive disorder found, in contrast, no differences in lymphocyte function between depressed patients and control subjects (Schleifer et al. 1985). Significant differences between patients and controls were revealed, however, when age, sex, severity of depression, and hospitalization were considered, with the most important and consistent effects found for age and symptom severity (Schleifer et al. 1985).

Mediating Mechanisms

In addition to establishing whether there is a relationship between psychological factors and health outcomes, research must identify mediating mechanisms. There are at least two biobehavioral path-

ways: the neural/neuroendocrine–immune pathway and the behavioral pathway. The latter consists of all of the habits and responses to situations that could have an impact, positive or negative, on health. For example, life stressors may result in increased or decreased physical exercise, alterations in sleeping habits, changes in diet and in use of alcohol, caffeine, nicotine, and drugs, and so forth. All of these behavioral states can have significant effects on the body's ability to maintain itself in good health and to resist disease. Most current psychoneuroimmunology research routinely monitors these behaviors, treating them either as covariates or as direct antecedents of immune changes. While most of the psychoneuroimmunology research that has examined behavioral response to stress has implicated the deleterious impact of these behaviors, some behaviors may have a positive effect on immune function and health and should also be recognized (Andersen et al. 1994; Temoshok and Dreher 1993).

Treating the behavioral pathways as covariates, most of the research in psychoneuroimmunology works with the neural/neuroendocrine–immune pathway, considering the physiologic alterations that eventually precipitate observable changes in immune function. The discovery of apparent association between levels and distribution of hormones and immune indicators has led to the presumption that the primary physiologic mechanism mediating cognitive activity and immune function involves neural impulses activating the neuroendocrine system, especially the limbic-hypothalamic-pituitary-adrenal (LHPA) axis. This model was reinforced both by the discovery of endocrine receptors on immune cell surfaces and by the discovery that some lymphocytes secrete endocrinologically active agents. This link with the neuroendocrine system enables the immune system to be involved in bidirectional interactions with the CNS (Dantzer and Kelley 1989; Rabin et al. 1989).

Although psychoneuroimmunology research has focused on the LHPA axis as the primary link between the CNS and the immune system, research on stress reactions involving the cardiovascular and other systems suggests that the involvement of the LHPA axis is not as simple as originally believed and that other neural

axes—involving the thyroid, anterior pituitary, and adrenal medulla—may also be involved in these reactions (Everly 1989). Different emotional reactions are accompanied by divergent hormonal patterns that are further affected by underlying personality characteristics (Jemmott et al. 1983).

A growing amount of research has demonstrated the covariation of levels of opioids, prolactin, growth hormone, adrenocorticotropic hormone (ACTH), and other hormones with immune indicators in addition to levels of the catecholamines and corticosteroids (Khansari et al. 1990; Maes et al. 1989; Rigatelli et al. 1993). These findings suggest the need for a broader assessment of endocrine and paracrine factors than is now accomplished in most psychoneuroimmunology studies. In addition, the discovery of complex communication networks within the immune system, involving cytokines that act as messengers between cells, provides the basis for the development of entirely new models of immune function that go beyond the early simple hormonal models. Elucidating the role of various emotional and affective states in differentially activating the various neural-hormonal axes will be important to the development of empirically based clinical interventions to reduce deleterious stressor and distress effects on immunity and health.

Assessment of Immune Function

In general, immune assays in humans can be categorized as either enumerative or functional. Enumerative methods involve total counts of peripheral blood white cells, which consist of polymorphonuclear leukocytes (PMN) and mononuclear cells. The latter comprise lymphocytes (T and B cells), monocytes, macrophages, NK cells, and large granular lymphocytes. The relative distribution of PMNs, lymphocytes, and macrophages can be differentiated on the basis of morphology. Each cell type can be phenotypically categorized on the basis of the expression of specific antigens, which are identified by simultaneous staining of peripheral blood mononuclear cells with antibodies that are conjugated to different fluorescent labels. The relative amounts of each subset are deter-

mined from the fluorescence intensities as measured by flow cytometry.

Functional assays include in vitro responses by lymphocytes to stimulation with either mitogens or antigens. Mitogens proliferate T and B cells polyclonally, whereas antigens act more specifically. T cell mitogens include concanavalin A (ConA) and phytohemagglutinin (PHA), whereas B cell mitogens include pokeweed mitogen (PWM). In a normally functioning immune system, memory cells for antigens such as tetanus toxoid are expected to be present, since the general population is exposed to such antigens. Responsiveness to a stimulus is determined by its ability to proliferate lymphocytes, usually detected by measuring newly formed DNA in the dividing cells. With the general trend toward use of nonradiolabeled compounds in the laboratory, proliferation can be measured by colorimetric assays.

Circulating immune cells have a normal distribution of quiescent and cycling cells. An abnormality in the immune system such as altered activation can be detected by studying the cell cycle status of immune cells. Cycling cells are usually identified based on incorporation of DNA-specific fluorochromes, detected by the fluorescence emission via flow cytometry. Increased DNA content implies cells are in S phase, and in these instances fluorescent intensity is amplified.

Other commonly used indicators of immune competence are NK cell activity and phagocytic functions of PMNs. NK activity is measured by the ability of the NK cells to lyse radiolabeled target cells. Killing efficiency of NK cells is measured by the percentage lysis at various effector–to–target cell ratios. Phagocytosis by PMNs is important in initial defense against pathogens, and therefore this parameter can be valuable in determining immune status. A commonly used assessment of PMNs involves challenging PMNs with a bacterium and then determining the amount of organisms phagocytized.

Soluble products, such as cytokines and immunoglobulins, are increasingly being studied. Because of the vast numbers of cytokines with overlapping inflammatory and other regulatory functions, these parameters add further complexity to research

studies. In addition, cytokines can modulate the neuroendocrine system (Blalock 1994), with inflammatory cytokines and the interferons being involved in the bidirectional neuroimmune connection.

Cytokine levels can be determined at either the messenger ribonucleic acid (mRNA) or protein level. Protein levels are assayed by means of cytokine bioactivity and immunoreactivity, while mRNA levels can be determined with Northern blots or the more sensitive nuclease protection assay. Cytokine mRNA is usually unstable, and low numbers of transcripts can be detected by reverse transcriptase polymerase chain reaction (RT-PCR) with specific primers. Unless the RT-PCR is quantitative, interpretation of the results should be viewed cautiously.

In spite of a growing ability to assess immune activity, the significance of the data with regard to immune competence is not always clear. Interpretation of any immune parameter should be viewed in the context of other parameters. Suppressed immune indicators are generally assumed to represent impaired immune function. However, increased levels of an immune indicator do not necessarily imply immunocompetence. Elevated immune parameters may result from a dysregulated immune system that can lead to pathological effects. For example, an increase in Epstein-Barr virus (EBV) antibody is generally assumed to indicate decreased immune function that has allowed latent EBV to become active, with this activation stimulating an increase in EBV antibody.

The meaning of enumerative measures is especially equivocal, particularly in light of tremendous variations in immune cell counts with no apparent clinical correlate (Cohen et al. 1991). Some functional assays can provide more meaningful information. For example, increased NK activity could mean that the person's body is capable of evading tumor cells. However, caution should be exercised when interpreting some functional assays. In vitro response to PWM does not necessarily mimic the in vivo response to a pathogen. As we have previously noted, most reported immune assays in human research are limited to immune cells obtained from peripheral blood and saliva because cells from lymphoid organs (secondary and primary) are essentially unavailable for ethi-

cal reasons (Kiecolt-Glaser and Glaser 1988; Schleifer and Keller 1991; Stein et al. 1990). Yet, based on knowledge from animal models, peripheral blood immune function is likely to be different from immune function in the lymphoid organs (Schleifer and Keller 1991). Elevated or lower levels of an immune measure in one body compartment (e.g., peripheral blood, regional lymph node, spleen) may be associated with cell trafficking and with increased levels in others. Although studies are beginning to focus on bone marrow cells (Rameshwar et al. 1993; Van Hagen et al. 1994), these studies have primarily addressed nervous system influences on blood formation. Studies in which environmental factors and other stressors influence the primary lymphoid organs are still lacking.

Drawing Conclusions in Psychoneuroimmunology Research

The complex nature of the immune system has resulted in a body of psychoneuroimmunology research that is similarly complex, involving numerous psychosocial antecedents, biobehavioral involvements, endocrine measures, immune indicators, and health outcomes. When one also takes into account the heterogeniety of study designs, the problem of drawing broadly based conclusions and generalizing results appears overwhelming.

Meta-analysis, a powerful statistical technique for integrating results of a number of studies (Glass 1976; Rosenthal 1993), has been increasingly utilized in research reviews. Through use of effect size and stability estimates, results from a number of studies are combined and average effect size and statistical significance are calculated; this provides a powerful and succinct quantitative summary of results from a number of studies. This approach is especially important for psychoneuroimmunology studies, given the generally small sample sizes and high costs of individual studies.

The first meta-analysis in the psychoneuroimmunologic literature appears to be that by Jemmott and McClelland (1989) on the effects of salivary IgA as an indicator of immune reaction to stressors and psychological states. An extensive meta-analysis on stressor-immune relationships (Herbert and Cohen 1993b) and an-

other on depression-immune relationships (Herbert and Cohen 1993a) were also conducted.

The increasing use of this technique suggests a need for greater awareness of its potential limitations. Subtle biases resulting from constrictive inclusion criteria can lead to the situation in which two meta-analyses of studies on the same topic draw opposing conclusions (see Rosenthal 1993 and Schmidt 1992 for detailed discussion of potential biases). There are often "holes" in the data—areas in which few, if any, studies have investigated some potential relationships (although an advantage of meta-analysis is its ability to highlight where these knowledge gaps occur). For example, Herbert and Cohen, in their reviews (1993a, 1993b), found a large number of research studies involving B cell and T cell counts and proliferative responses but, with the exception of studies of herpesvirus antibodies, relatively few involving cytokines and B cell–derived plasma cells. The requirement that the immune indicator be examined in at least three studies for inclusion in these meta-analyses resulted in the exclusion of studies using more recent techniques, such as cytokine indicators (e.g., interleukin-1, interleukin-2, leukocyte inhibitory factor).

Caution must also be maintained in making generalizations from meta-analyses because findings concerning what appears to be a continuum (e.g., young vs. older patients) sometimes come from distinctly different studies (e.g., some on old patients, others on young patients), each using different methods, selection criteria, and so forth (Goodkin and Feaster 1998; Goodkin et al. 1998; Lelorier et al. 1997; Moher and Pham 1999). Furthermore, interactions and moderator effects among variables, so common in psychoneuroimmunology studies, are in many cases poorly handled in meta-analyses because of the lack of an adequate number of studies involving these interacting variables.

Stress and Immunity

Evidence that the immune system is responsive to psychological states first came from research involving the effects of life stressors

on immune function and from behavioral conditioning studies (see Ader et al. 1991 for review). Animal research has demonstrated that a variety of stressors can alter immune processes and that the relationships among stressor, immune function, and behavior are complex (Keller et al. 1983, 1988; Monjan and Collector 1977).

Several reviews of the research literature on the relationship between stress and immune function in humans have appeared (Calabrese et al. 1987; Herbert and Cohen 1993b; Kiecolt-Glaser and Glaser 1991; O'Leary 1990). As noted earlier, life stressor research is complicated by two factors: stressors can be characterized in many different ways, and distinct types of stress are associated with different immune reactions. Four different taxonomies of stress can be found in the reviews by Kiecolt-Glaser and Glaser (1991), O'Leary (1990), Cohen and Williamson (1991), and Herbert and Cohen (1993b). The nature of the relationships among stressors and immune indices will vary to some extent depending on the particular taxonomy being used. Despite these limitations, there is substantial evidence for a relationship between stress and functional immune measures, enumerative measures, and immunoglobulin levels.

In addition to evaluating the overall effect of stress, Herbert and Cohen (1993b) examined stressor effects as assessed as measured by observability of the stressor (stressor defined as an observable event) and duration (long-term vs. acute laboratory stressor) and social nature (interpersonal stress vs. nonsocial stress) of the stress. Stress in general was associated with decreases on all functional measures included in the meta-analysis (i.e., ConA, PHA, and NK cell activity). Nonsocial stress was associated with decreases in PHA and NK cell activity; interpersonal stress tended to be the least potent of the stressors. Interpersonal/social stressors may affect different components of the immune system than does nonsocial stress. Short-term and objective events had an especially strong effect on NK cell activity. In terms of the enumerative measures, stress was associated with decreases in B cells, T cells, and NK cells and an increase in total white blood cells. CD8+ cells tended to be most sensitive to stress, showing a stronger associa-

tion with objective events than was found for the other enumerative measures monitored. In addition, long-term stress had a strong inverse relationship with CD8+ cells; however, the opposite relationship existed for short-term stress (i.e., acute laboratory stressors) (Herbert and Cohen 1993b).

Antibody titers to latent herpes simplex virus and EBV have frequently been demonstrated to increase substantially in the presence of stressors, and this suggests a down-regulation of the immune system that allows activation of some latent viruses (Herbert and Cohen 1993b; O'Leary 1990). Immunoglobulin levels are elevated in the presence of stressors, but, in an interesting anomaly, whereas plasma IgA was elevated in the presence of short-term and nonsocial stress, salivary IgA appears to have been suppressed under similar circumstances (Herbert and Cohen 1993b). These anomalous findings may reflect methodologic issues in measuring salivary IgA. Furthermore, at least one study showed changes in salivary IgA and plasma IgA in the same direction (Green et al. 1988).

Other reviews of the effects of stress on immune function take somewhat different approaches to the literature but tend to come to the same conclusion: stress, defined in a variety of ways, affects immune measures (Calabrese et al. 1987; Cohen and Williamson 1991; O'Leary 1990). One of the most frequently implicated immune effects of stressors involves suppressed NK cell counts and function, a finding that may have important implications for our understanding of cancer prognosis (Andersen et al. 1994) and HIV-disease progression (Solomon et al. 1993).

Depression and Immunity

As with the stress literature, a number of reviews of the depression-immune literature have appeared (Calabrese et al. 1987; Herbert and Cohen 1993a; Miller et al. 1991; Schleifer and Keller 1991; Stein et al. 1991a, 1991b; Weisse 1992). Some disagreement exists in these reviews as to the nature and extent of the impact of major depression on immune function. Stein and colleagues (1991a) drew

the conclusion that effects are erratic and are often not found. However, Herbert and Cohen (1993a) came to the opposite conclusion using formal meta-analytic techniques, as did Weisse (1992) in a review of studies of bereavement and social disruption involving both human and nonhuman models. Possible explanations for this discrepancy among major reviews lie in the analytic technique used, the number of studies covered, the number of immune measures considered, and the nature of the subjects and mood dysfunction included in the studies reviewed.

A distinction is usually made in the literature between clinical depression and depressed mood, with the majority of studies examining clinical depression. In general, clinical depression appears to be reliably associated with decreases in all of the measures of lymphocyte function, including proliferative responses to PHA, ConA, and PWM. In addition, NK cell activity is significantly lower in clinically depressed persons. Herbert and Cohen (1993a) concluded that "these four effects [decreased proliferative responses to PHA, ConA, and PWM and decreased NK cell activity] were particularly robust, and their size impressive" (p. 480). In addition, they noted that among clinically depressed patients, severity of depressive symptoms was moderately associated with reductions in functional measures. Age and hospitalization were notable moderators of the overall relationships found and are discussed in more detail below.

Findings for enumerative measures tend to parallel those for functional measures, with clinical depression being associated with lower counts of B cells, total T cells, helper T cells, cytotoxic/suppressor T cells, and large granular lymphocytes/NK cells (Herbert and Cohen 1993a). At the same time, however, clinical depression was found to be associated with significant increases in total white blood cell counts, total monocyte counts, and, especially, total neutrophil counts. Antibody titers to herpesviruses (herpes simplex virus 1 and cytomegalovirus) were substantially elevated in the presence of clinical depression, a finding suggestive of increased antibody activity as a result of compromised immune function that permitted latent viruses to replicate. As with the functional immune measures, age and hospitalization

were major moderators of the effect of depression on enumerative measures.

The moderating effect of age is emerging as an important factor in understanding the relationship between depression and immune function. We have previously drawn attention to the role of age in this relationship (Schleifer et al. 1989a), and more recent research from our laboratories (Andreoli et al. 1993; Rigatelli et al. 1993; Schleifer et al. 1994), as well as work by other researchers (Evans et al. 1992; Maes et al. 1989), continues to support the importance of age as a major explanatory variable in the effects of depression on immune function. Herbert and Cohen (1993a) noted that suppressed immune cell function and counts were substantially more evident in older patients. Greater reduction in cell counts was found among older subjects than among the full range of patients, with effect sizes approaching zero among younger patients in all cases. Hospitalization status provided similar results on decreased measures. One problem with these findings, noted by Herbert and Cohen, is the overlap between hospitalization and age, making it difficult to determine which is the causative factor.

Why age and hospitalization act as moderators in the immune-depression relationship cannot be directly inferred from studies to date. For example, age could reflect a change in the organic capability of the body over time, but it could also reflect a change in coping style as one ages. For example, we (Schleifer et al. 1987) found preliminary evidence that in older bereaved men immune suppression occurred shortly after bereavement, whereas in younger bereaved men there appeared to be a delayed and exaggerated immune reaction to bereavement. This difference in timing of the bereavement reaction is consistent with biological aging effects and with different coping styles in younger and older men. Similarly, hospitalization could be an indicator for any number of factors that are the true mediators of the relationship between depression and immune function. For example, hospitalization results in changes in sleep patterns, diet, and intake of alcohol, caffeine, and nicotine, to mention just a few mediating health-related behaviors.

Role of Other Affective States in Stress-Related Immune Changes

In addition to depressed mood, other affective states, such as anxiety and anger, may influence immunity. Kemeny and colleagues (1989) found anxiety and hostility to be negatively associated with numbers of CD8+ cells, but not CD4+ cells, in healthy subjects infected with herpes simplex virus. In a study of cancer patients, Fawzy and colleagues (1993) found that NK cell percentage and interferon-augmented NK cell activity were associated inversely with anxiety and depression and directly with anger. Growing evidence demonstrates the connection between arousal-type mood states and increased endocrine activity, with the latter possibly having a direct impact on some immune functions. For example, Malarkey and colleagues (1994) found that hostility in newlywed couples was associated with increased levels of plasma epinephrine, norepinephrine, growth hormone, and ACTH.

Preliminary studies from our laboratory suggest that affective states such as anger and anxiety may be associated with immune changes opposite those found with depression. In our studies of family members of trauma victims during the first week after the trauma (e.g., motor vehicle accident, gunshot), we found that lymphocyte function, although not associated with exposure to the stressor per se, was related to the affective state of the subjects (Schleifer et al. 1989b). Multiple regression analyses showed that depressive symptoms were related to decreased ConA response, while anxiety symptoms in the same sample were associated with increased mitogen response.

In another study, we have been investigating the psychoneuroimmunology of healthy adolescents living in an inner city with substantial stressful conditions. Initial analyses of psychological, social, and immunologic data for more than 300 adolescents revealed that depressive symptoms were associated with decreased mitogen (ConA and PWM) responses, whereas perceived life stress was linked to increased PWM response (Keller et al. 1992). We also found that adolescents reporting more aggressive behaviors had relatively increased lymphocyte mitogen responses and NK cell ac-

tivity (Bartlett et al. 1989). In addition, the extent to which anger was expressed, as indicated by self-reported aggressive behaviors, modified the relationship between anger and immune function (Bartlett et al. 1994).

The possibility that the changes in immune function associated with various affective states may be opposite in direction from those associated with depression as a whole necessarily raises the conceptual issue of the clinical diagnosis of depression and the specific symptoms associated with depression. Most research has focused on major depressive disorder as a whole, but subgroups of major depressive disorder (e.g., bipolar, endogenous) do not always show the same relationship to immune function as does major depressive disorder (Stein et al. 1991b). Of equal concern is that the diagnosis of depression is based not only on reports of depressed affect but also on symptoms such as irritability, anxiety, and insomnia, which may be independently associated with immune function in ways dissimilar to the way major depressive disorder per se is associated with immune function. The presence of comorbid disorders in major depressive disorder, such as panic disorder, has been shown to moderate the relationship between major depressive disorder and immune function (Andreoli et al. 1992; Schleifer et al. 1994).

Alterations in Immune Function Resulting From Changes in Mood and Stress Reactions

The growing evidence that stressors and mood affect immunity has led to an interest in the possibility that interventions to help manage stressors or mood may also modulate immunity. Norman Cousins's attempt to cure his illness through humor (Cousins 1979), and research suggesting relationships between positive mood and coping styles in cancer progression (Levy et al. 1991; Temoshok and Dreher 1993), have added to this interest. A provocative study involving the use of several meditation techniques demonstrated a dramatic reduction in mortality over a 3-year period among elderly nursing home patients who practiced medita-

tion every day (0% mortality) in comparison with control subjects (40% mortality) (Alexander et al. 1989).

Most stressor reduction interventions generally involve helping a person to achieve a state of "relaxation," but the techniques can be quite varied, and this raises the issue of whether the same psychological state is being achieved. In two recent reviews of stress-reduction interventions and immune function (Halley 1991; Van Rood et al. 1993), the "relaxation" techniques in the reviewed studies included progressive muscle relaxation, focused breathing, guided imagery, various meditation techniques, massage, lying quietly with eyes closed, saying "so" and "hum" on inhalation and exhalation, biofeedback, hypnosis with and without immune-altering suggestion, and viewing a humorous film. Kiecolt-Glaser and Glaser (1992) described additional psychological interventions, including conditioning, self-disclosure, and psychotherapy. Fawzy and colleagues (1990a, 1990b, 1993) conducted a randomized controlled clinical trial of a 6-week intensive group psychotherapy focused on coping strategies to adapt to stress. As mentioned earlier, they found that the intervention patients had significantly higher interferon-α-augmented NK cell activity 6 months after the intervention (Fawzy et al. 1990b). At 6 years' follow-up, the intervention group had significantly fewer recurrences and deaths (Fawzy et al. 1993).

The majority of studies have focused on immune parameter changes, but the variety of relaxation techniques and immune measures used make concise generalizations difficult. At present, research on the effectiveness of psychological interventions on immune function is sparse and can be characterized as, at best, "limited but promising" (Kiecolt-Glaser and Glaser 1992). Interestingly, in light of all the research on interventions to reduce stress, almost no research has been reported in which immune modulation has been examined as a function of interventions to manage depression, whether depressed mood or major depression. One study found that treatment of depression with mianserin resulted in decreased depressive symptoms as measured by the Hamilton Rating Scale for Depression and a simultaneous increase in neutrophil activity (O'Neill and Leonard 1986; cf. Weisse 1992).

Conclusion

Evidence indicating that stress and depression are connected to changes in immune function, based on both functional and enumerative measures, is strong and growing. However, the relationships among the variables are complex and still not fully understood. For example, the effect of stress appears to vary as a function of whether it is chronic or acute and whether it involves interpersonal relationships or is nonsocial in nature. We and others have demonstrated that age plays an important role in mediating these relationships, to such an extent that failure to account for age can be expected to obscure or distort potential relationships. Individuals over the age of 60 are much more likely to have depressed immune function in the presence of depression or stressors than are younger people. Although evidence is less conclusive, gender and hospitalization status also appear to be emerging as important moderators in psychoneuroimmunological relationships. Until recently, affective states other than depressed mood have received little attention in psychoneuroimmunology research. A small body of research has emerged that suggests that emotions such as anger and fear may have immune effects that may be opposite those associated with depression. More research in this area is clearly needed.

The amount of research that has directly addressed the connection between immunity and disease is still very limited, but enough well-controlled studies have demonstrated this link to increase its viability in explaining changes in health in situations of even relatively minor stressors or mood alterations (Keller et al. 1994).

The current state of the psychoneuroimmunology research literature can be characterized as one of many disparate findings uncomfortably existing side by side with very little theory to integrate these findings. The application of meta-analytic techniques such as those used by Herbert and Cohen (1993a, 1993b) provides an important first step in organizing the many findings into coherent models. Other emerging models include those of Cohen and Williamson (1991) and Andersen and colleagues (1994), although more

detail with regard to specific immune effects in these models is still needed. Integration of the growing body of existing but disparate research findings into coherent theoretical models is an important task in a young and growing field.

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Chapter 2

Behavioral States and Immune Responsiveness

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Much new data over the last decade demonstrate that the central nervous system (CNS) plays an important role in the modulation of aspects of immune function. Numerous preclinical studies indicate that certain forms of stress may result in alterations in aspects of immune status. As with the CNS modulation of other systemic homeostatic processes (e.g., blood pressure regulation), basic experimental investigations are beginning to determine CNS pathways involved in the neural modulation of immune physiology (Ader et al. 1991). Experimental evidence indicates that the limbic-hypothalamic-pituitary-adrenal (LHPA) axis and sympathetic nervous system (SNS) are the two primary immunomodulatory pathways subserved by the CNS (Ader et al. 1991; Morley et al. 1987). Although the specific central circuitry has not been fully elucidated, neural modulation of immune activity appears to involve the limbic forebrain and cortical regions (Felten and Felten 1987). These brain structures are intimately associated with the control of affective and emotional processes as well as the modulation of the activity of the LHPA axis and descending sympathetic autonomic pathways that innervate immune organs (e.g., spleen).

Despite advances in the field of psychoneuroimmunology, the relationships among clinical psychiatric syndromes, neurobiology,

and immune status are not well understood (Herbert and Cohen 1993; Stein et al. 1991). This may, in part, stem from differences in variables across studies, including duration of symptoms, temporal parameters (e.g., when samples are drawn for assays), and subject variables such as gender, age, and heritable personality characteristics. An understanding of how these variables may interact to produce changes in immune responsiveness may be of particular importance for the design of clinical psychiatric investigations in psychoneuroimmunology. Such studies include those aimed at elucidating the neurobiological mechanisms that underlie immune changes associated with various stressful psychological processes. Moreover, such information may help in the design of studies seeking to clarify whether particular neuropsychiatric conditions (e.g., major depressive disorder) influence the progression of immune-mediated disease states, including human immunodeficiency virus (HIV) spectrum illnesses.

In this chapter, we present data from both clinical and basic science studies that address some of these important questions. Because excellent reviews of the animal and human psychoneuroimmunology literature are available elsewhere (Ader et al. 1991; Herbert and Cohen 1993; Kiecolt-Glaser and Glaser 1991, 1995, 1998; Solomon 1987; Stein et al. 1991), our objective in this brief chapter is not to comprehensively review the literature. Rather, we wish to present some of our clinical and preclinical data that may help to delineate several important factors most relevant to an understanding of the complex interactions operative in the psychoneuroimmunology of stress, mental disorders, and health.

Effects of Behavioral States on Immune Function

Nearly three decades ago, Solomon and colleagues (1968) performed their classic study demonstrating that early experience could produce long-term changes in immune function in rodents. Subsequently, other pioneering investigations, including those of Ader and Cohen (1982), provided powerful demonstrations of the relationships among the CNS, behavior, and immune function. By

pairing saccharin (a conditioned stimulus) with an immunosuppressant, cyclophosphamide (an unconditioned stimulus), Ader and Cohen (1982) behaviorally conditioned mice so that later exposure to saccharin alone resulted in immunosuppression and altered the course of murine systemic lupus erythematosus. Subsequent animal studies, by Lysle and colleagues (1990), established that conditioned environmental stimuli (inherently nonaversive stimuli) previously paired with an aversive event (foot shock stress) can themselves induce pronounced immunosuppression. These and many other basic studies in psychoneuroimmunology have provided the basis for clinical studies examining the effects of psychiatric syndromes, in particular major depressive disorder, on immune status.

Research over the last decade has shown that some parameters of immune status may be altered in patients with major depressive disorder (for reviews, see Herbert and Cohen 1993; Stein et al. 1991). For the most part, these studies have largely focused on mitogen-stimulated T cell responses, natural killer (NK) cell activity, and enumerative differences in lymphocyte subsets (via flow cytometry). As indicated by a recent meta-analysis (Herbert and Cohen 1993), the most consistent immune changes associated with major depressive disorder have been reductions in NK cell activity and mitogen-induced T cell proliferation. However, there are also data suggestive of autoimmune or inflammatory processes in depressed patients (Maes et al. 1991, 1999). Indeed, as Stein and colleagues (1991) emphasized in their review of this literature, there is ample evidence of conflicting results among the available studies. In what follows, we discuss several factors that may account, in part, for some of these conflicting findings in the literature.

Behavioral Traits and Immune Function: Preclinical Studies

Investigations in psychoneuroimmunology conducted over the last three decades have focused on understanding how various stressful, nonsocial (e.g., foot shock, paradigms of learned helplessness), and social states (e.g., bereavement, social conflict) may

alter immune function in animals and humans (Ader et al. 1991). Despite much theorizing that stable personality characteristics (e.g., introversion vs. extroversion) may predispose humans to certain immune-based diseases, such as some types of cancer (Fox 1978; Hagnell 1966), few experimental studies have examined whether heritable behavioral "traits" are related to immune responsiveness. Likewise, little is known about how behavioral states and traits interact to influence immune status.

Selective breeding has been used in animal studies to investigate the genetic basis and neurobiological mechanisms that underlie behavioral traits such as alcohol sensitivity, open-field activity, and emotionality. Selective breeding is a powerful research strategy that can be used to study how genetics (genotype) interacts with developmental and experiential factors to produce individual differences (phenotype). Several studies in rodents found that selective breeding for differences in behavioral traits, including alcohol-induced sleep time (Petitto et al. 1990) and active avoidance behavior (Sandi et al. 1991), resulted in associated differences in parameters of immune function. However, the relation of differences in social traits to immune function and predisposition to the development of certain diseases has not been systematically investigated.

Understanding the relation of heritable or stable social behavior to immune function in animal models may be especially important to understanding the complex interactions between stress and/or mental disorders on immune status and health in humans. Using two lines of outbred Institute for Cancer Research (ICR) mice that were selectively bred and carefully studied over multiple generations for differences in social behavior, we have begun to address directly this important, fundamental question in psychoneuroimmunology.

In their studies of social behavior, Cairns and colleagues at the University of North Carolina have selectively bred outbred (genomically heterogeneous) ICR mice for differences in isolation-induced aggression (Cairns et al. 1983; Gariepy et al. 1988). These mouse lines are referred to as the NC selected lines. This genetic selection has produced a line of mice (NC100) that fail to

show the isolation-induced aggression typical of this strain but exhibit high levels of immobility or freezing in response to social contact. Conversely, mice from the high aggressive line (NC900) show the expected high levels of isolation-induced aggression typical of this strain. Our studies with the NC selected lines were the first to demonstrate directly that genetic differences in social behavior (traits) may be associated with individual differences in NK cell activity, T cell responses to mitogen stimulation, and interleukin-2 (IL-2) and interferon production (Petitto et al. 1994). Our experiments also show that low aggressive or socially inhibited (NC100) mice are more susceptible to 3-methylcholanthrene-induced tumor development (Petitto et al. 1993b). Our efforts are now focused on how genetic and experiential factors during early development interact to result in these marked line differences in immune status.

In addition, as mentioned earlier, although a considerable body of data attests to the potency of various behavioral states on immune function, few studies have examined the issue of how state-trait interactions affect immune function. Thus, we are also beginning to use this valuable mouse model to determine how heritable differences in social behavior (traits) and specific stressful social contexts or states interact to produce changes in immune function (and correlated changes in neurobiology). We believe that our preclinical data and other data of this nature may be critical to greater understanding of the relation of social behavior and immune function in humans. Moreover, such knowledge may ultimately provide important insight into why similar psychosocial or environmental factors sometimes result in the development or progression of immune-mediated disease states (e.g., human immunodeficiency virus 1 [HIV-1] infection) in some individuals but not others.

Altered Diurnal Changes in Immune Parameters in Major Depression

Subsets of circulating lymphocytes exhibit different circadian (or ultradian) rhythms (Haus et al. 1983). This is one reason why it is critical to standardize the time of day when samples are drawn for

immune assays in comparisons of subject groups (e.g., depressed vs. psychiatrically healthy comparison groups). Preclinical studies indicate that immunological rhythms may be entrained to CNS rhythms (Ottaway and Husband 1992). It is well established that circadian (or ultradian) rhythms are often disrupted in major depression (Halaris 1987) and that these depression-related rhythm abnormalities include parameters of neural and endocrine function implicated as immunomodulators (e.g., cortisol, melatonin, estimates of noradrenergic activity).

In an initial test of this hypothesis, we compared circulating NK cell phenotypes and NK cell activity in patients with major depressive disorder and nondepressed control subjects at 8 A.M. and 4 P.M. during the same 24-hour period. These times approximate the diurnal peak and nadir, respectively, of NK cell functional activity in healthy individuals on a schedule of nocturnal rest and diurnal activity (Gatti et al. 1988). We found that, compared with the control subjects, patients with major depressive disorder exhibited significantly reduced diurnal variation in levels of Leu-11 NK cells and NK cell cytotoxic activity between 8 A.M. and 4 P.M. (Petitto et al. 1992). Subsequently, we found that diurnal variation in surface Ig+ (sIg+) B lymphocytes was also disrupted in patients with major depressive disorder (Petitto et al. 1993a). These marked diurnal differences were significant when variation was assessed both as the change in actual number of sIg+ cells and as the percentage of sIg+ cells of total lymphocytes.

Having made these initial observations of diurnal variation at only two time points, it was now important to compare these parameters of NK cell function, as well as other immune measures, in groups of patients with major depressive disorder and nondepressed comparison groups at multiple time intervals (e.g., every 3 hours). Such comparisons would permit a direct test of the hypothesis of circadian (or ultradian) group differences. It is noteworthy that seasonal changes in immunologic rhythms and other biological rhythms have been reported (Haus et al. 1983). Therefore, we have studied both healthy comparison and depressed subjects together in parallel to control for any group potential differences due to season.

In our two initial studies, we found that differences between pa-

tients with major depressive disorder and nondepressed control subjects in terms of the immune measures tested (e.g., NK cell activity, sIg+ B lymphocyte levels) were more pronounced in the early morning than in the late afternoon. For example, reductions in NK cell activity in the depressed patients were observed in the morning, a finding consistent with those from a number of investigations that have compared depressed and control subjects in the morning. These differences were statistically significant at the highest effector–to–target cell ratios measured but not across all five of these ratios (likely because of the small sample size). However, in the same sample, when NK cell activity was compared at 4 P.M., the subjects with major depressive disorder as a group did not exhibit lower levels of NK cell activity. In fact, these patients actually had higher levels of NK cell activity at 4 P.M. than the nondepressed comparison subjects (although this difference was not statistically reliable across the five effector–to–target cell ratios). Interestingly, similar relationships were observed by Miller and colleagues (1991) when they assessed NK cell activity in patients with major depression and nondepressed control subjects in the early afternoon. They found that the depressed patients also had higher NK cell activity than the control subjects. These differences were statistically significant at three of the five effector–to–target cell ratios. Together these data indicate that basal NK cell activity is not decreased or increased exclusively in depression. Rather, we postulate that patients with major depressive disorder may exhibit altered NK cell chronobiological rhythms (e.g., phase shifts). Thus, different outcomes between the existing studies may be explained, at least in part, by the timing of the samples (i.e., whether samples were obtained in the morning or the afternoon).

An investigation by Martini and colleagues (1988) showed that asymptomatic HIV-infected individuals may manifest disruptions of the normal CD4 (T helper) cell circadian cycle that may predate both symptoms of HIV-spectrum disease and, in some instances, reductions in CD4 cell counts. Since HIV infection affects the CNS as well as the immune system, it is possible that disrupted CD4 circadian rhythms are secondary to chronobiological changes in the CNS.

Effects of Gender on Depression-Related Changes in Natural Killer Cell Function

In humans, there is evidence that females live longer than males (a pattern supported by evidence from studies with other species) and that mortality rates associated with bereavement and coronary heart disease are lower in females than in males (Jacobs and Ostfeld 1977; Stoney et al. 1987). In addition, males may be more vulnerable to certain immune-related diseases such as serious bacterial infections and many types of cancer, as well as some immunodeficiency syndromes (Adami et al. 1990; Purtillo 1977; Purtillo and Sullivan 1979; Washburn et al. 1965). Certain behavioral stressors also result in greater elevations in LHPA axis cortisol responses and sympathetic activation (e.g., sympathoadrenal catecholamine and systolic blood pressure response changes) in males than in females (Frankenhaeuser 1983; Matthews and Stoney 1988). These findings suggest that stress and depression may differentially affect parameters of immune function in males and females. To date, however, few preclinical or clinical studies have determined systematically if immunologic responses to "stress" differ between the sexes.

In a large study examining the effects of major depressive disorder on peripheral blood NK cell phenotypes and NK cell activity (Evans et al. 1992), we found that males with major depressive disorder showed marked reductions in blood levels of NK cell phenotypes (CD16 and CD57) and NK cell activity compared with healthy male control subjects. By contrast, females with major depressive disorder did not differ significantly from healthy female control subjects on these NK cell parameters. Although several potential contributing factors cannot be ruled out (e.g., smaller female sample size, a possible floor effect among females), these results support the hypothesis that major depressive states differentially alter measures of NK cell function in males and females. In our study, we obtained blood samples in the early morning. Consistent with our findings are those of Irwin and colleagues (1987, 1990b), who demonstrated across studies that, compared with male control subjects, depressed male veterans show reductions in NK cell

activity (in the morning). Interestingly, Miller and colleagues (1991), comparing NK cell activity in depressed patients and nondepressed control subjects, also found gender differences in changes associated with depression. In the early afternoon, they observed that depressed female patients had higher NK cell activity than did female control subjects; depressed male patients and male control subjects did not differ on this measure.

It will be important in future investigations to assess systematically NK cell measures and other parameters of immune status in depressed subjects in order to determine whether the syndrome of major depression has differential effects on immune responses in males and females. It has been postulated that these sex differences in immune function and cancer susceptibility may be mediated by sex hormones, particularly estrogens (Adami et al. 1990). NK cell activity has been reported to vary cyclically with the estrous cycle in animals, although the data are less clear in human studies, which report both estrous cycle–related NK cell activity changes and no differences as a function of the estrous cycle. In our initial study, we were not testing a priori for depression-related sex differences in NK cell function. Thus, it will also be important in future investigations to account for differences in phase of the estrous cycle as well as oral contraceptive status (although the literature suggests that oral contraceptives do not significantly affect CD16+ or CD57+ lymphocyte levels) (Baker et al. 1985). Likewise, although no consistent alterations in pituitary-gonadal axis activity have been reported in depressed male patients compared with matched control subjects (Rubin et al. 1989), it is possible that adrenogenic steroid–associated immune changes also contributed to the immune changes observed in the depressed males in our sample.

Conclusion

Despite advances in psychoneuroimmunology, the relationships among clinical psychiatric syndromes, neurobiology, and immune status are not yet well understood. As our data from both clinical

and basic studies illustrate, this ambiguity may stem, in part, from factors such as temporal parameters (e.g., timing of drawing samples for assays) and subject variables (e.g., sex and heritable personality characteristics). Other methodologic variables, such as the subtypes of patients being studied (e.g., melancholic vs. nonmelancholic major depressive disorder patients, patients with major depressive disorder that is recurrent vs. those experiencing a first episode) and duration of symptoms (e.g., depressed patients with symptoms of several weeks' duration vs. patients with treatment-resistant depression with symptoms of several months' duration), require attention in future studies.

Clarification of how these factors or variables interact to produce changes in immune responsiveness is of particular importance in designing informative clinical studies. For example, because clinical investigations aimed at relating changes in aspects of immune function to major depression have resulted in ambiguous findings, the progress of mechanistic studies attempting to identify neural and neuroendocrine mechanisms that may underlie immune changes has clearly been impeded. Before one can reliably delineate the responsible mechanisms, it is critical to have a reproducible phenomenon to study.

Animal models can be valuable in that they permit mechanistic studies critical to the generation of testable hypotheses concerning the mediation of immune alterations that often accompany stressful life events or clinical mood disorders. An excellent example of such studies comes from the research of Irwin and colleagues (1991). These authors found that blood levels of neuropeptide Y, a modulatory peptide co-released with norepinephrine during SNS activation, correlated inversely with NK cell activity in a group of hospitalized patients with major depressive disorder. This observation is a logical extension of their previous preclinical studies in which they demonstrated that the SNS is involved in the neural mediation of immune function during some forms of stress relevant to depression (Irwin et al. 1990a). Likewise, understanding how stable "personality" traits are related to immune status and interact with behavioral states to alter immune responsiveness and disease susceptibility is of particular importance in under-

standing the complex interactions between behavior and immune outcome in humans.

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Chapter 3

Cervical Cancer: Psychosocial and Psychoneuroimmunologic Issues

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The role of psychosocial factors in the course of different types of cancers is still the subject of controversy. A review of the literature leads to the preliminary conclusion that the number of studies lending no support to a possible influence of psychosocial factors in oncogenesis equals or even exceeds the number of studies yielding positive results (Goodkin et al. 1993a, 1993b). However, there are important methodological differences among studies, and a wide variety of factors have been studied. Psychosocial concepts commonly studied include stressful life events, distress, social support, coping, and personality. These differences between studies make a direct comparison across different studies and the drawing of overall conclusions a precarious undertaking.

In addition, it appears that specific aspects of psychosocial status may contribute to progression depending on the cancer. Cancers

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differ considerably in the extent to which their progression is under the influence of immunologic and hormonal factors. This is a particularly important issue because in psycho-oncology the endocrine and immune systems are generally considered to be the mechanisms by which psychosocial processes may extend their influence to oncogenesis and tumor progression. For example, hormonal factors are known to directly play a prominent role in breast and prostate cancer, whereas the immune system is considered to make a primary and significant contribution to the onset of malignant melanoma (Cohen et al. 1987).

Cervical cancer—worldwide, the second most common form of cancer in women—is another example of a cancer in which the role of immunosurveillance is substantial. The plausibility of this connection is supported by the fact that viruses, particularly oncogenic types of the human papillomavirus (HPV), are involved in the development of cervical dysplasia. In addition to an established role for immunosurveillance, a more pragmatic aspect of studying psychosocial influences on cervical cancer is that several precancerous (i.e., dysplastic) stages can be identified histologically with high reliability and validity. The accessibility of the cervix to examination and regular screening procedures with Pap smears further contributes to the feasibility of detecting such precancerous stages. Finally, in contrast to many other types of cancer, the influence of familial or genetic factors is weak or absent in invasive cervical cancer (Goodkin et al. 1993a). Thus, there are several reasons for taking a multidisciplinary approach to cervical oncogenesis and the progression of premalignant lesions, variously referred to as *cervical dysplasia, cervical intraepithelial neoplasia* (CIN), and, most recently, *squamous intraepithelial lesions* (Figure 3–1).

In this chapter, we discuss epidemiologic and screening issues in cervical cancer as well as several psychosocial and psychoneuroimmunologic issues pertaining to its etiology. A discussion of the pathology of CIN, the etiological role of viral infections, and associated psychoneuroimmunologic issues, as well as a review of studies of the prevalence of cervical cancer (including the influence of race, socioeconomic status, age, and marital status), is presented. In addition, the results of Dutch screening studies on cervical cancer,

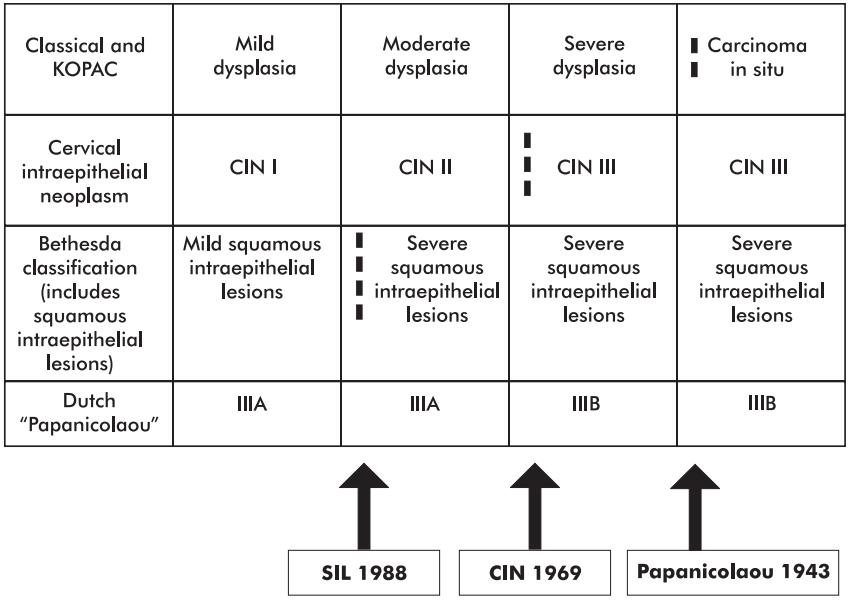

Figure 3–1. Classifications of lesions that are precursors of invasive cervical cancer. Terminologies are displayed, along with the years they were introduced (in boxes at bottom of figure). SIL = squamous intraepithelial lesion. The thick black dashes refer to different boundaries for the stage at which active treatment, rather than follow-up with observation, is recommended. As can be seen, this boundary has been moving to earlier disease stages over time. KOPAC refers to a classification system widely used in the Netherlands: *K* refers to the quality of the smear (thickness too great or gross blood); *O,* to microbiological flora and viral changes; *P,* to the presence of squamous cell abnormalities (mild, moderate, severe; carcinoma in situ; microinvasive carcinoma; invasive carcinoma, by histologic rather than cytologic terminology); *A,* to miscellaneous factors; and *C,* to the presence of abnormalities of the cervical endothelium (as with *P,* also in histologic terminology). The differentiation of Class IIIA from Class IIIB in the "Dutch" Papanicolaou classification represents a separation by cytologic grading of less severe cellular atypia (consonant with mild and moderate levels of dysplasia by histology) from more severe cellular atypia (consonant with a more severe level of dysplasia or with invasive carcinoma).

Source. Reprinted from Boon ME, Suurmeijer AHJ: *The Pap Smear.* Leiden, the Netherlands, Coulomb Press, 1993, p. 106. Used with permission.

in which the importance of the role of general practitioners is stressed, are summarized. Attention is paid to the consequences of screening outcome for the overall well-being of the participating women. The core of this chapter is the discussion of the potential role of psychosocial factors—including health behaviors, stressful life events, social support, and coping styles—on the progression of precancerous cervical lesions to invasive squamous cell carcinoma of the cervix. Finally, we present the results of a Dutch pilot study on psychosocial aspects of CIN. Information is provided regarding the complex interplay of factors arising from different domains of functions in the development of this disease. Suggestions are offered for methodologically sound future studies in this important field of research in women's health.

Pap Smear, Cervical Intraepithelial Neoplasia, and Sexually Transmitted Diseases

In 1928, George Papanicolaou reported, in Battle Creek, Michigan, his chance observation that cervical cancer cells can be found in a vaginal smear (Papanicolaou 1928). (Victor Babes, a Romanian pathologist, had introduced cytologic sampling of the uterine cervix at least 2 years earlier [Babes 1928].) In his later collaboration with the gynecologist H. F. Traut, Papanicolaou found cells from many malignant cervical tumors that were not suspected clinically. This large series of cases was published in Papanicolaou and Traut's classic monograph of 1943, *Diagnosis of Uterine Cancer by the Vaginal Smear.* They realized that this method could be used to recognize cervical carcinoma in its early stages so that it could be promptly treated. This observation offered prospects for effective prevention of this kind of cancer through, as envisioned by Papanicolaou and Traut, mass screening of women prior to the development of invasive cancer. Since the name Papanicolaou was considered to be too long, the terms *Pap test* and *Pap smear* were introduced for this screening procedure. (The procedure involves a scraping of the external opening of the cervix and the posterior vaginal arch.) Although such screening has not eradicated cervical carcinoma, it is perhaps still one of the most effective cancer screening tests available.

Several HPV types commonly found in genital infections ("high risk" types) have been shown to play a role in the development and promotion of dysplasia in the cervix. The overall prevalence of HPV increases from 70% in Pap smears indicating mild to moderate dysplasia, to 84% in smears indicative of severe dysplasia, to as much as 100% in smears with carcinoma in situ. HPV high-risk types (in particular, types 16, 18, and 33) are nearly always present in invasive tumors (Lungu et al. 1992; Zur Hausen 1991). In addition, there are indications that their presence may be associated with the rapid progression of CIN. On the other hand, preliminary data suggest that progression rarely occurs when there are no signs of infection by these high-risk or other, intermediate-risk HPV types.

It has been suggested that herpes simplex virus 2 (HSV-2), as well as other pathogens known to be causes of sexually transmitted diseases (including *Trichomonas vaginalis, Neisseria gonorrhoeae,* and *Treponema pallidum* [syphilis]), also plays a role in the initiation or the promotion of CIN. However, subsequent studies overall did not confirm the early hypothesis that HSV-2—formerly the strongest candidate other than HPV—plays a role in inducing cervical oncogenesis (Zur Hausen 1991).

Nevertheless, there is some evidence that the presence of certain pathogens other than HPV (e.g., Actinomyces) is associated with an increased risk of CIN. However, *Candida albicans* has been found to be related to decreased risk of CIN (Boon and Suurmeijer 1993). Until recently, little was known about the precise nature of these etiological associations. It is likely that lifestyle is an important factor in the presence of these microorganisms in the vaginal flora, since it is well established that lifestyle is a factor in the epidemiology of cervical carcinoma (Goodkin et al. 1993a).

Prevalence and Incidence of Cervical Intraepithelial Neoplasia and Invasive Cervical Cancer

Despite the dramatic fall in mortality rates in the Western world, cervical cancer remains a serious health concern, with an expected prevalence of 16,000 cases in the United States. Regarding the epi-

demiology of HPV and CIN in the Netherlands, we refer to Van den Brule et al. 1991. The prevalence rates of HPV types 16 and 18 in cytologically abnormal Pap smears have been observed to be 70% (van den Brule et al. 1991), and this suggests that this proportion or more of women with CIN have high-risk HPV types. The decreased incidence of invasive cervical cancer worldwide has been ascribed to the introduction of cervical screening programs. With the development of reliable, inexpensive, and relatively noninvasive procedures such as the Pap smear and colposcopy, methods for the early detection of precancerous lesions have become widely available. For example, in Scandinavia, the nationally coordinated screening program has resulted in a reduction in mortality from cervical cancer of 30% to 60%. However, in England, where adherence to screening programs is haphazard, mortality from this disease has been reduced very little over the past 20 years (Course Team U205 1985; Foster 1995).

An increased incidence of CIN (precancer or "dysplasia") has been reported for younger age groups (individuals less than 35 years of age) worldwide. The modal age at diagnosis of CIN has decreased from the middle 30s to 24 years (Campion et al. 1988). This trend holds primarily for CIN of lower levels of severity; the incidence of severe CIN has decreased dramatically over the past 15 years. In the Netherlands, the modal age range for carcinoma in situ is 30 to 34 years and for severe dysplasia, 25 to 29 years. These decrements in age among those diagnosed with CIN have become an issue of great medical concern. In response to these decrements, the screening policy in the Netherlands—where screening had been restricted to the age range of 35 to 55 years—was adjusted to include younger women. Initiation of screening relative to sexarche (e.g., 5 years after first coitus) deserves serious consideration. On the other hand, spontaneous regression reportedly occurs rather frequently, especially in young women (less than 30 years of age) with lower levels of severity of CIN (Meijer et al. 1992).

Race and Ethnicity

Much as with other diseases, the prevalence of cervical cancer shows considerable variation among races and ethnic groups.

A relatively high prevalence has been reported among African Americans and Hispanic Americans (in particular, Panamanians, Colombians, Chileans, Peruvians, and Cubans), as well as Greenlanders. Groups at low risk for this cancer include Amish, Jewish, Irish, and Italian Americans (Goodkin et al. 1993a). Since there are strong associations among cultural factors, other sociodemographic factors, and individual behavioral factors known to be related to cervical oncogenesis (e.g., age at first coitus, access to health care, cigarette smoking [De Vet and Sturmans 1994], sexual habits of consorts, and genital hygiene), it is often assumed that the interactions among these factors explain the cultural differences observed in the frequency of cervical cancer. However, cultural factors may also have an independent role in the prevalence of cervical cancer. As a case in point, an Indonesian study (Harahap 1986) showed no associations between cervical cancer cases and well-known risk factors (e.g., age at first coitus, frequency of coitus, multiple partners). The findings from this study raise the possibility that cultural factors sometimes also act independently of other known social and behavioral risk factors.

Age

As with other types of cancer, the incidence of cervical cancer is higher with increasing age. However, as already noted, the age at which a CIN diagnosis is typically established has been decreasing worldwide. In addition to chronological age, the menarche (age at first menstruation), sexarche (age at first sexual contact), and the age at first pregnancy are important foci. In a study by R. K. Peters and colleagues (1986), the interval between menarche and the first coitus appeared to be substantiated as an important protective factor. Moreover, A. A. W. Peters and Trimbos (1994) found an absence of indices of HPV infection in sexually nonactive women. However, these types of protective (or risk) factors generally are rather labile in statistical analyses, and their effect may depend onthe extent to which other, related factors are taken into account.

Marital Status

Research by Dutch investigators has revealed that the rate of abnormal Pap smears is dependent, in particular, on marital status. The prevalence of abnormal Pap smears in urban settings was more than three times as high as that in rural settings (7.1 cases per 1,000 persons vs. 2.2 cases per 1,000 persons). This finding may be explained by the remarkable differences in marital status across settings. Compared with married women (4.5 cases per 1,000 persons), widowed and divorced women, more frequently living in urban settings, had substantially higher rates of abnormal Pap smears (7.6 cases and 16 cases per 1,000 persons, respectively).

It is tempting to speculate about the underlying mechanisms responsible for these impressive epidemiologic differences. It has been established that divorced and widowed individuals have decreased immunologic measures (Bartrop et al. 1977; Goodkin et al. 1996a, 1996b; Kiecolt-Glaser et al. 1987a) and higher morbidity and mortality ratios for a wide variety of diseases (Schaefer et al. 1995; Stroebe and Stroebe 1993). Such observations are generally seen as indirect evidence of the role of psychosocial factors—in particular, life stressors and depression—on carcinogenesis and infectious disease. The extent to which the very high incidence among the divorced is additionally associated with their sexual activity level—or that of their ex-partners'—remains to be established.

Socioeconomic Status

Several of the aforementioned sociodemographic factors are related to the socioeconomic status of women at risk for invasive cervical cancer. The socioeconomic status of women is, in turn, closely related to their spouse or partner's occupation. In the Netherlands, the socioeconomic status of a woman is often closely correlated with the occupational level of her partner. Apart from the lifestyle factors discussed earlier (e.g., age at first coitus, cigarette smoking, genital hygiene), the partner's occupation and associated level of exposure to potential carcinogens may be important. Robinson (1982) showed that the women most at risk were those married to

workers with extensive exposure to dirt and dust, such as miners, quarrymen, furnace men, and other occupations (including fishermen and members of the armed forces). These data suggest that chemicals or irritants are transmitted by sexual intercourse. Together with the smegma, which itself has been shown to have carcinogenic potential, these industrial pollutants may significantly affect the course of CIN.

Cervical Cancer Screening: The Dutch Experience

Cervical cancer is theoretically almost entirely preventable. Insight into the possible role of psychosocial factors in determining the onset and course of cervical cancer may contribute to the development of preventive strategies. Pap smear screening is one of the oldest of these preventive measures. In the Netherlands, general practitioners (GPs) have been greatly involved in obtaining Pap smears from their patients since the early 1970s (Boon and Suurmeijer 1993; Boon et al. 1982). It is important to stress that almost every woman in the Netherlands has a GP, because the GP is the central provider of Dutch health care. GPs have been the key figures in centrally organized cervical screening in the Netherlands since 1989.

If screening is defined as every woman in a certain age group having the opportunity to obtain a Pap smear, we cannot speak of a specific screening program in the Netherlands prior to 1989, since the decision to obtain a Pap smear from patients during office visits was made by the GPs on a patient-by-patient basis. However, in 1976 a nationwide cervical cancer screening program was established in the Netherlands (Evaluation Commission 1989; Habbema et al. 1985; Van Ballegooijen et al. 1992a; Van der Graaf et al. 1986, 1988a, 1988b). Women between 35 and 55 years of age received an invitation to be seen by health screening teams for the purpose of having a Pap smear once every 3 years—a rate less frequent than in the United States, where once per year is the norm. In the design of this program, the role of the GP was limited to making a referral to

a gynecologist in cases in which an abnormal Pap smear was detected. This program was discontinued in 1985 because of a curtailment of government funding. By that time, 370,000 women in six regions had been screened at least twice at a 3-year interval (Boon et al. 1987). Only in one major city, Leiden, was this type of Pap smear screening continued into a fourth screening round, with a positive rate for severe dysplasia or invasive cancer of 1%—a quarter of that in the first round (Boon et al. 1990).

In the nationwide Pap smear screening program started in 1989, in which a Pap smear was obtained once every 3 years, every woman between 35 and 55 years of age received scheduled visits to have a Pap smear taken by her own GP. For a proper evaluation of Pap smear screening programs, one must know not only the cytological diagnosis but also the follow-up histological diagnosis (by cervical biopsy) obtained for all women with a cytological diagnosis of mild or more severe dysplasia. All patients with a cytological diagnosis of severe dysplasia, carcinoma in situ, or invasive squamous cell carcinoma were referred for colposcopy, biopsy, and, if indicated, treatment. Some of the patients in this group had been diagnosed previously as having mild or moderate dysplasia at the time of initial screening, but during follow-up more severe lesions were detected. All histological reports were traced by using the Dutch Network and National Database for Pathology, and these findings were confirmed by calling the GPs. Tissue from all biopsies was sent to pathology laboratories in Leiden.

Participation Rate in Dutch Screening Programs

Across both Leiden programs—the non-GP program that was carried out between 1976 and 1985 and the GP program established in 1989—approximately 55,000 women were canvassed. In the non-GP screening program, the participation rates varied from a low of 26% in the city of Leiden to a high of 58% in some small villages. In the GP program, the participation data were processed by the local municipalities, which reported a participation rate of 31% in the city of Leiden and as high as 67% in some villages. The rate of participation in the GP program was 43% versus 37% in the

non-GP program. These overall participation rates are much lower than those obtained when screening was started in the 1970s (Evaluation Commission 1989; Kirk and Boon 1981) and far from the hypothetical 65% used in the cost calculations of Van Ballegooijen and colleagues for the Netherlands (Van Ballegooijen et al. 1992a, 1992b; Van Oortmarssen et al. 1992).

In the city of Leiden, where nonparticipation was investigated by the local municipality, 44% of the nonparticipating women replied that they had already had a Pap smear taken in the previous year by their GP, 17% had had a total hysterectomy, and 19% had already been to their gynecologist for a Pap smear. Only 5% of the nonparticipating women replied that they were not interested in having a Pap smear done. In the city of Leiden, 3% of the women screened were born in foreign countries, mainly in Morocco and Turkey. In this group, participation in the GP program was much lower (22% for the Moroccan women and 16% for the Turkish women) than that for Holland-born women of the city of Leiden (34%), analogous to the lower participation rates found among African Americans and Hispanic Americans.

In the non-GP screening program in Leiden, the participation rate among the divorced women was considerably lower than that among the married women (Boon and Beck 1991). This phenomenon was also observed in other Dutch regions (Boon and Suurmeijer 1993). Furthermore, the enthusiasm of the divorced group to continue participating decreased disproportionately when the GPs were not involved (Boon et al. 1990), as witnessed by the low rate of participation (18%) in the fourth round. For the married group in the city of Leiden, participation stabilized after the second round, with a participation rate of about 36%. As was expected, the divorced women, a group known to be at high risk for invasive cervical cancer (see Boon et al. 1987, 1990), were underrepresented in the non-GP program. The participation rate of the divorced women in the GP program was almost twice that in the non-GP program, whereas the participation rate of the married women was approximately the same—a finding indicative of the overall utility of the GP program for increasing screening rates of women at risk.

Prevalence of Abnormal Cytology on Pap Smears

The positive cytology rate (severe dysplasia, carcinoma in situ, and invasive carcinoma) increased from 1.00 to 3.40 cases per 1,000 persons when the GPs were involved (Table 3–1). In the GP screening program (1989–1995), 104 women were referred to the gynecologist for a biopsy. Forty women had a histological diagnosis of severe dysplasia, and 26 more had the diagnosis of carcinoma in situ. Two of the in situ carcinomas were of glandular origin (adenocarcinoma in situ) and therefore were not relevant to the squamous cell lesions under study here. It was striking that the six invasive squamous cell carcinomas were detected exclusively in the GP screening program. The positive histology rates for severe dysplasia, carcinoma in situ, and invasive carcinoma were significantly higher in this program.

Table 3–2 shows the positive cytological rates in both programs stratified by age. In both screening programs, not surprisingly, the highest rates were found in the young age group (35–39 years) and the lowest in the two age groups of 45–49 and 50–54 years. For all four age groups, the cytological rates in the GP screening program were higher than those in the non-GP group. When the positive histological findings of the GP program were stratified by age (Table 3–3), it was found that five of the six invasive carcinomas occurred in women under the age of 45 years. For severe dysplasia and carcinoma in situ, the highest rates were in the age group 35–39 years. Table 3–4 presents the cytological data of the GP program stratified by degree of urbanization (rural, semirural, and urban). Not surprisingly, the highest rates were found in the cities, and the lowest rates were found in the rural areas.

Comparison of GP and Non-GP Screening Programs

When the results of non-GP and GP cervical cancer screening programs in the Netherlands are compared, it is evident that the more recently developed GP screening program yielded remarkably higher positive screening rates, both for cytology and for histology. We conclude, therefore, that groups of women at high risk for cer-

Table 3–1. Positive cytology and histology rates (per 1,000 persons) in the two screening programs for cervical cancer in the region of Leiden, the Netherlands

	GP screening (n = 19,104)[a]	**Non-GP screening (n = 19,981)[a]**	z
Cytologic diagnosis[b]			
Severe dysplasia or higher	3.40 (65)	1.00 (20)	3.43*
Histologic diagnosis			
Severe dysplasia	2.09 (40)	0.60 (12)	4.04*
Carcinoma in situ	1.36 (26)	0.35 (7)	3.43*
Invasive carcinoma	0.31 (6)	0.00 (0)	2.50*

Note. Rates for the GP screening program were from the period 1989 to 1995. Rates for the non-GP screening program were from the period 1976 to 1985. GP = general practitioner.

[a]Numbers in parentheses represent the number of positive cases of the physicians participating.

[b]Mild and moderate dysplasia data are not shown.

*Significant at $P \leq 0.05$.

vical cancer are better reached by the GP screening program, since the greater number of women at high risk participating implies that more positive cases will be detected. Perhaps, a GP is in a better position to convince at-risk women to agree to a Pap smear. Since financial reimbursement for Pap smears was minimal in the Netherlands during the years under study here—GPs received only £4.00 (about $2.10 in 1999 U.S. dollars) per case for their screening endeavors—it may be assumed that financial reimbursement played only a minor role in yielding the high GP screening rates observed in these years.

The participation rate in both screening programs was low. In the non-GP screening program, both the physician and the office (health care center) were unfamiliar to the patient. This circumstance may have been associated with increased examination-

Table 3–2. Positive cytology rates (per 1,000 persons) in the two screening programs for cervical cancer in the region of Leiden, the Netherlands, stratified by age

	GP screening		Non-GP screening		
Age range (years)	**Rate[a]**	**No. of smears**	**Rate[a]**	**No. of smears**	***z***
35–39	4.43 (28)	6,316	1.23 (8)	6,498	3.42*
40–44	6.68 (22)	5,973	1.10 (7)	6,353	2.95*
45–49	2.13 (6)	2,812	0.64 (2)	3,122	1.56
50–54	2.25 (9)	4,002	0.75 (3)	4,008	1.73

Note. Rates for the GP screening program were from the period 1989 to 1995. Rates for the non-GP screening program were from the period 1976 to 1985. GP = general practitioner.

[a]Numbers in parentheses represent the number of positive cases of the physicians participating.

*Significant at $P \leq 0.05$ or greater.

related anxiety, which may have inhibited many of the "high risk" women from participating. In the GP program, the main reasons for not participating were valid ones (e.g., a Pap smear had been taken 1 year prior to the program, or the woman had had a total hysterectomy). The attendance of divorced women in the GP program, compared with that of divorced women in the non-GP program, was higher by a factor of two, and we assume that for the GP-screened women the threshold to seek the GP for this test is lower than would be inferred from the overall participation rate and yet again lower than would be inferred from the non-GP participation rate (with its less familiar environment and personnel). This relatively higher rate within the GP screening program for divorced women compared with that for married women may have been the result of an overall tendency for the former to visit their GP more often. However, divorced women represent only 12% of the population, and this implies that the increase in detection rates

Table 3–3. Positive histology rates (per 1,000 persons) in the general practitioner screening program for cervical cancer in the region of Leiden, the Netherlands, 1989–1995, stratified by age at screening

Age range (years)	Severe dysplasia[a]	Carcinoma in situ[a]	Invasive carcinoma[a]	No. of smears
35–39	3.01 (19)	2.85 (18)	0.16 (1)	6,316
40–44	2.01 (12)	1.17 (7)	0.67 (4)	5,973
45–49	1.78 (5)	0.00 (0)	0.36 (1)	2,812
50–54	1.00 (4)	0.25 (1)	0.00 (0)	4,002

[a]Numbers in parentheses represent the number of positive cases of the physicians participating.

Table 3–4. Cytology rates of severe abnormalities (per 1,000 persons) in the general practitioner screening program for cervical cancer in the region of Leiden, the Netherlands, 1989–1995, by urbanicity

Municipality	Rate
A (rural)	1.72
B (semirural)	3.79
C (urban)	4.60

cannot be explained solely by the greater attendance of this high-risk group. Nevertheless, we may conclude that favorable shifts in participation occurred when the GP became the pivotal focus of the screening program. However, the low participation rate of Turkish and Moroccan women in the Netherlands, as well as that of minority group women cross-culturally, still needs further attention from the medical community. These low rates relate to sociocultural barriers to minority group participation in regular cervical cancer screening both in the Netherlands and in the United States.

◆

In conclusion, in the Netherlands, participation in the GP program led to better detection of cervical pathology in women than participation in a nationwide, direct outreach screening program. The involvement of the GP clearly adds value to screening program efficacy compared with screening by non-GPs. We therefore concur with Havelock (1990) in strongly recommending the involvement of GPs in cervical cancer screening programs in countries like the Netherlands in which GPs play a gatekeeping role in the health care system.

Psychological Distress Related to Pap Smears

Women with a cytological diagnosis of severe dysplasia or invasive cancer are routinely referred directly to a gynecologist for colposcopically directed cervical biopsy and, if indicated, further treatment. Thus, in a short period of time, they know exactly what treatment is required and how successful the treatment is. However, women with a positive Pap smear indicative of only mild dysplasia are not so treated but instead are asked to return in 3 months for a repeat Pap smear. If the repeat Pap smear proves to be negative, they are asked to return in 1 year for another repeat Pap smear. If the Pap smear at that time is positive for cytological abnormality, they are referred directly to the gynecologist for colposcopically directed cervical biopsy and, if indicated, further treatment. This procedure confers a risk of psychological morbidity for women with mild dysplasia in that they may remain uncertain for a prolonged period of time about whether a clinically significant lesion is present.

How do women cope with this situation of chronic uncertainty? Van der Vugt (1994) sent a relevant questionnaire to 129 women with a cytological diagnosis of mild dysplasia. The response rate was 78%. The data were stratified according to the final histological diagnosis: D+ (subsequent dysplasia) and D– (no sub-

sequent dysplasia). It is important to note that in more than 60% of the cases, these mild dysplastic lesions regressed spontaneously and were never confirmed by a subsequent histological diagnosis, since they were of a transient nature. Thus, D+ might better be characterized as persistent or progressive dysplasia, and D– as "transient" dysplasia. The D+ and D– groups were different in several ways. The D+ group answered more frequently that they 1) were very worried about the upcoming follow-up care (77% vs. 44%), 2) were still worried after such follow-up care (though not as much as the D– group) (18% vs. 34%), and 3) did not think of themselves as completely cured when the cytology results became negative (16% vs. 7%). These findings indicate that, on the whole, over the entire follow-up period women with persistent or progressive dysplasia experienced greater levels of psychological distress than did women with dysplasia of a transient nature.

The results of another study—a Dutch pilot study involving 26 women visiting a clinic with an abnormal Pap smear prior to follow-up care and histological diagnosis—also indicated patients' strong concerns about cancer (Visser et al. 1995). The women in this sample estimated (on a scale of 0 to 100%) their chance of having cancer after an abnormal Pap smear to be, on average, 26%. A quarter estimated their chance to be less than 25%, but a third estimated their chance to be greater than 50%. The answers on a question concerning the amount of stress caused by the abnormal Pap smear (score 0–100) yielded a mean score of 56; about a quarter scored below 50, and another quarter scored above 75—a finding similar to that reported in the United States by Lerman and colleagues (1991) for cervical cancer screening. Of interest, those patients who were later diagnosed as having CIN II or III (moderate or severe dysplasia, respectively, requiring treatment) expressed a significantly higher level of "perceived stress" before diagnosis than did the low-risk group (those having no CIN or having CIN I) (Visser et al. 1995). These results highlight the need to carefully control for perceived stress at the time of the abnormal Pap smear in studies aimed at elucidating a relationship between prior psychosocial status and the etiology of this disease.

Psychosocial and Behavioral Factors Related to Cervical Intraepithelial Neoplasia and Cervical Cancer

The studies reviewed earlier in this chapter indicate the possibility that lifestyle and behavioral factors—in particular, those associated with sexual behavior—influence the initiation and promotion of CIN to invasive cervical cancer. The presence of oncogenic HPV types is known to be associated with decreased cellular immune system measures. This implies that the cellular immune system—and, indirectly, those psychosocial factors that appear to modulate cellular immune system function—may contribute to the progression or the regression of CIN.

Over the past 15 years, the relation of psychosocial factors, including life events, social support, and coping styles, to the development of CIN and invasive squamous cell carcinoma of the uterine cervix has been studied at the University of Miami. In a total of three distinct samples, a semiprospective design was used to assess women awaiting the results of colposcopically directed cervical biopsy after an abnormal Pap smear (Antoni and Goodkin 1988, 1989; Goodkin et al. 1986, 1993a, 1993b, 1993c, 1993d). The first and the third studies yielded closely corresponding results. A greater number of stressful life events with a negative impact was associated with a higher grade of CIN. In the first study, this association over the prior 6 months was significantly increased by pessimism, hopelessness, somatic anxiety, "life threat reactivity" (an index of autonomic responsivity to a given severity of stressor), and social alienation (which may be thought of as related to decreased social support). The second study showed that a passive/helpless coping style, characterized by an overly respectful and cooperative relationship with authority figures, was more directly associated with an increased grade of CIN.

Interestingly, another study examined alexithymia—a personality trait indicating difficulty with emotional expression and comparable to overly respectful and cooperative coping style. This trait, like a passive/helpless coping style, has been associated with an increased likelihood of dysplasia. Further, alexithymic subjects

had lower cytotoxic T lymphocyte counts than did nonalexithymic subjects, and alexithymic subjects with dysplasia had lower CD4 cell counts than did nonalexithymic subjects with dysplasia (Todarello et al. 1994). More recently, this group reported a replication of this study, fully confirming those results (Todarello et al. 1997).

On the basis of these findings, a psychosocial model for the etiology of cervical cancer has been proposed—one that, as our foregoing results document, requires testing in a prospective and longitudinal design. In this model, explicit and detailed attention is paid to potential confounding factors. The most important of these factors are HPV type, cigarette smoking, frequency of prior Pap smears, one's own suspicion of having cancer, perceived distress at the time of notification of the abnormal Pap smear, diet (vitamin A, folate, and selenium intake), number of sexual partners before age 20, number of partners of the male consort (the "male factor"), educational level, socioeconomic status, and marital status (cf. Goodkin et al. 1993a, 1993b).

In addition, a recent study of 52 HIV-1-seropositive African American, Haitian, and Caribbean English-speaking women showed a relationship of higher pessimism with lower natural killer (NK) cell cytotoxicity and a lower percentage of suppressor/cytotoxic T lymphocytes (CD3+CD8+), controlling for presence of high-risk HPV type, subjective impact of life events, and lifestyle factors affecting immunity (Byrnes et al. 1998).

The literature reviewed in the subsections that follow pertains to the study of the relationship between psychosocial factors and the course of CIN. First, we review studies showing that psychosocial and behavioral factors may affect immunity. Second, we address studies demonstrating a relationship between immune function and the development and course of CIN. Third, we discuss studies that have found an association between psychosocial factors and CIN or cervical cancer. Finally, we summarize the results of a Dutch pilot study of the relationship between psychosocial factors and CIN grade, which have given impetus to a recently begun longitudinal prospective study of these psychosocial factors, in which the role of immune measures as mediators is being examined (Visser et al. 1995, 1996, 1998).

Psychosocial and Behavioral Factors Affecting Immunity

In the last decade, there has been increasing scientific research supporting the hypothesis that life stressors are associated with immunologic decrements (Herbert and Cohen 1993; Kiecolt-Glaser and Glaser 1991). Stressors identified include major stressors such as bereavement (Bartrop et al. 1977; Goodkin et al. 1996a, 1996b; Irwin et al. 1987, 1988; Schleifer et al. 1983), caretaking for patients with Alzheimer's disease (Kiecolt-Glaser et al. 1987b), separation and poor marital quality (Kiecolt-Glaser et al. 1987a, 1988), as well as relatively minor stressors such as medical school examinations (Kiecolt-Glaser et al. 1986). Furthermore, additional studies have shown that accumulation of several (micro-) stressors reflected in high scores on life stressor surveys or daily hassles questionnaires (Brosschot 1991; Jemmott and Locke 1984) is likewise associated with such immunologic decrements.

Some studies (Brosschot 1991; Jemmott and Locke 1984) have specifically addressed the issue of controllability and have shown that perceived lack of control is related to lower levels of immune measures, although another study (Weisse et al. 1990) reported findings from an acute laboratory reactivity setting that failed to support this view.

Social support (Levy et al. 1990) and active coping style (Goodkin et al. 1992a, 1992b) have both been found to be related directly (i.e., positively) to levels of NK cell cytotoxicity, among other immune measures (e.g., active coping style and CD4 cell count). Also, loneliness was associated with an increase in Epstein-Barr virus viral capsid antigen antibody titers, a finding reflecting impaired cellular immunosurveillance, increases in viral replication, and resultant increases in circulating antibody. Other factors—particularly cigarette smoking, alcohol consumption, recreational substance use, exercise, sleeping habits, prescribed medication use, caffeine intake, sexual activity level, and diet—have been shown to affect immune status (Goodkin et al. 1993a, 1993b; Kiecolt-Glaser and Glaser 1988).

It is clear that further research is required to establish what ef-

fects life stressors, social support, and coping style have on immunity in relation to promotion of CIN.

Immune Function and the Course of CIN

The results of a body of research strongly support the mediation by the immune system in the progression of CIN (Goodkin et al. 1993a, 1993b). First, it should be stressed that virus-induced cancers, in general, have been shown to be more antigenic than other forms of neoplasia, and thus their clinical course may be more dependent on the immunocompetence of the host (Keast 1970; Reif 1975). Several studies have shown an association between the presence of HPV types 16, 18, and 33 (along with a few other intermediate risk HPV types) and grade of CIN (Lungu et al. 1992; Meisels and Morin 1990; Van den Brule 1991; Zur Hausen 1982). There is strong evidence suggesting that the involvement of these HPV types in CIN contributes to the pathogenesis of cervical cancer. The presence of high-risk HPV types in a considerable proportion of cervical smears with dysplasia (70%–80%) and in a low proportion of cytologically normal smears (3.5%) confirms that HPV in the former smears may be considered a strong risk factor for the development of cervical cancer.

Zur Hausen (1982) has advanced a specific application of the "initiation-promotion model" (Berenblum 1941) for cervical cancer. In this model, HPV infection is hypothesized to have a promoting role in cervical carcinogenesis, while a HSV-2 infection is thought to most likely have an initiating role. Although recent studies have failed to provide clear evidence of a role for HSV-2 in cervical cancer (see Zur Hausen 1991 for review), several studies do suggest a potential role for HSV-2 in the etiology of this tumor (Dexeus et al. 1988; DiPaolo et al. 1990; Reeves et al. 1985). Yamakawa and colleagues (1994) showed that HSV-2 can be a co-factor in cervical carcinogenesis in HPV-infected women. This association was more prominent in Indonesia than in Sweden.

Several factors must be considered when interpreting the available findings on immune function and the course of CIN. First, HPV infection alone is known to cause abnormal Pap smears

(Kreider et al. 1985; Zur Hausen 1991). Second, pharmacologically immunosuppressed organ transplant recipients (Penn 1986) and women infected with human immunodeficiency virus 1 (HIV-1) (Provencher et al. 1988), compared with sociodemographically matched immunocompetent control subjects, show a severalfold increase in risk for CIN and cervical cancer. Third, CIN and invasive cancer are associated with changes in several systemic and local immune parameters. These parameters include activated cytotoxic CD8+ T lymphocytes (specifically reactive to HPV-associated antigens in association with major histocompatibility complex [MHC] class I molecules) (Melief and Kast 1990, 1991), CD4 cell count (Castello et al. 1986), CD4:CD8 ratio, lymphocyte proliferation stimulated by the mitogen phytohemagglutinin, NK cell count and cytotoxicity, antibody-dependent cell-mediated cytotoxicity, serum immunoglobulin levels (predominantly IgG, IgA, and IgM levels), squamous cell carcinoma antigen, and specific antibodies to the early regulatory (rather than structural) proteins of HPV high-risk types (e.g., E6 and E7).

It may be concluded that immune measures are related to high-risk–type HPV infection and the course of CIN. Some immune measures may also be affected by psychosocial factors (i.e., life stressors, social support, and coping style). Hence, a synergism may be observed.

Associations Between Psychosocial Factors and CIN

A limited number of studies have directly examined the role of psychological factors in CIN progression and cervical cancer. However, most of these studies were hampered by serious methodological drawbacks, such as use of a retrospective design, inadequate control for relevant biomedical or social risk factors, and lack of objective measures (Goodkin et al. 1993a, 1993c). In what follows, we summarize the most important findings.

Schmale and Iker (1971) applied a semiprospective design to predict "cancer" and "no cancer" correctly in 50 of 68 asymptomatic women interviewed after repeated class III Pap smears but be-

fore the results of biopsy were available. These authors' central concept was "hopelessness potential," but, unfortunately, no objective measure was utilized. Spence and colleagues (1978) counted words referring to hope and hopelessness in the interviews conducted as part of Schmale and Iker's study and found both a relative increase in hopeless words and a decrease in hopeful words in the cancer group. A major problem of this study is that the patients representing cases and noncases differed in terms of some important sociodemographic characteristics.

Pancheri and colleagues (1979) compared cervical cancer patients with healthy control subjects and women with uterine "fibroids" (i.e., benign tumors)—all of whom were aware of their diagnosis. Although the cervical cancer patients did show increased state anxiety and depression as well as increased use of repression and denial, these responses may, in fact, have been reactions to the diagnosis itself.

Evans and colleagues (1986) demonstrated a high rate of major depressive disorder among gynecologic cancer patients, including those with cervical cancer. Further, they found that both tumor load and weight loss were associated with cortisol levels after administration of dexamethasone in the dexamethasone suppression test, a possible indication of a role for the limbic-hypothalamic-pituitary-adrenal axis in progression of cervical carcinoma.

The Miami studies discussed at the beginning of this section were the first to focus explicitly on grades of CIN as well as invasive cervical cancer. It is important to note the correspondences as well as the differences in findings between the University of Miami studies (Goodkin et al. 1993a, 1993b) and those of Pancheri et al. (1979) regarding passive coping on the one hand and between the University of Miami studies and those of Schmale and Iker regarding hopeless attitudes on the other hand. Taken together, these investigations lend support to the hypothesis that both "internal" psychological variables (e.g., coping style) and "external" variables (e.g., life stressors and their controllability, social support) moderate CIN progression.

Finally, a study by Graham and colleagues (1971) deserves attention because of the large number of subjects enrolled. A large

sample of cervical cancer patients (n = 447) were compared with control subjects with other cancers or a variety of benign diseases (n = 711) by means of a double-blind interview technique. No differences with respect to life stressors were found. However, the study did not include healthy control subjects. In addition, the psychological test measures and statistical tests on which the authors' conclusions were based were not described.

Dutch Pilot Study of Psychosocial Factors in CIN

Methods

We conducted a pilot study on the association between level of CIN and several psychosocial factors (Visser et al. 1995). The level of dysplasia was determined by histology (i.e., pathology reports of cervical biopsy specimens). The study was conducted at three gynecologic oncology clinics where women were regularly followed up for abnormal Pap smears. Twenty-six women completed a psychosocial questionnaire on lifestyle (e.g., smoking, alcohol consumption, use of recreational substances, eating habits), gynecologic history (e.g., Pap smear frequency, suspicion of cervical cancer, sexual habits), and psychosocial factors. The psychosocial factors assessed were coping style (assessed by the Utrecht Coping List [Schreurs et al. 1984] and COPE [Carver et al. 1989]), life events (Life Experience Survey; Sarason et al. 1978), social support (Social Support Questionnaire; Sarason et al. 1983), and distress (Profile of Mood States; McNair et al. 1971). These data were collected before the biopsy results were communicated. Complete data were available for 22 women.

Results

All women had an abnormal Pap smear class (90% with class III and 10% with class IV). The distribution of CIN level by histology was as follows: no CIN, 15%; CIN I, 31%; CIN II, 19%; and CIN III, 19% (missing cases n = 4). Comparison of the low-risk group (no

CIN or CIN I) and high-risk group (CIN II or CIN III) yielded the following results.

Sociodemographic variables. In most cases, the women were of Dutch nationality (91%). Nearly two-thirds (63%) had a low level of education. Most were married or living together (89%), and just under half were employed (44%). The women in the high-risk group belonged to a younger age group (31.3 years vs. 39.9 years).

Health behaviors. About half of the women were smokers (54%); the mean number of cigarettes smoked per day was 8.5. About a quarter of the women reported insomnia. Most of the women used alcohol (80%); the mean number of glasses of alcohol per week was 7. The gynecological history indicated that only one woman admitted to having had a sexually transmitted disease, although 50% reported having had vaginal infections. The mean number of prior Pap smears was 6. The high-risk group reported a longer time since their last normal Pap smear than did the low-risk group.

Sexual intercourse first occurred at a mean age of 18 years. Between ages 14 and 20 years, the women with sexual experience had had, on average, three different sexual partners. Most of the women (83%) did not report condom use during intercourse in the 6 months prior to assessment. Of note, the high-risk group, compared with the low-risk group, had a three times higher total number of prior sexual partners.

Psychosocial factors. The high-risk group, relative to the low-risk group, was found to have less expression of emotions (as assessed by the Utrecht Coping List) and to be less oriented to problem solving (as assessed by the COPE). The high-risk group also had a less active coping style, a stronger tendency toward denial, more mental distraction, and more palliation than the low-risk group (as assessed by the COPE). The high- and low-risk groups did not differ in terms of social support and life events, including the total number of negatively rated life events. The high-risk group did have higher distress scores on the Profile of Mood States than did the low-risk group.

Prospective Study on Psychosocial Factors as Predictors of CIN

The results of the Dutch pilot study described in the preceding subsection generally confirmed the expected health behavior, sexual habits, coping styles, and life event burden of women at risk to develop severe CIN or invasive cervical cancer. These results, in conjunction with the empirically supported theoretical model based on prior research by one of us (K.G.), are being used as the groundwork on which to base a prospective study of the potential of psychosocial factors for predicting the course of CIN (Visser et al. 1996). The aim of the study, which will involve a large sample of women, is to investigate the potential of psychosocial factors (coping style, social support, and stressful life events) for predicting the severity level (the first part of the study) and course (the second part) of CIN. On the basis of a psychosocial model developed from prior work, it is hypothesized that having experienced negative, uncontrollable, unpredictable, and chronic major life event stressors over the prior 6 months, in conjunction with inadequate and unsatisfactory social support and use of a more passive coping style (as opposed to an active coping style, such as planning a strategy and taking action), is associated with a greater likelihood of CIN progression.

In Part I of the study, women having received notification of an abnormal Pap smear and HPV infection of the cervix with high risk (16, 18, 33) and low-risk oncogenic types will be evaluated in terms of the following psychosocial factors: 1) life event stressors experienced over the prior 6 months (including controllability, predictability, and perceived duration), 2) social support (including availability and satisfaction), and 3) coping styles (to distinguish between passive and active coping). This approach will be used to reveal any association with grades of dysplasia (CIN I, CIN II, CIN III, and invasive cervical cancer compared with HPV infection without CIN [control group]).

In Part II, women from Part I who have been diagnosed with CIN I or CIN II and have HPV infection with high- or low-risk oncogenic types will be approached concerning enrolling in a lon-

gitudinal, prospective study to determine relationships of the same set of psychosocial predictors with the same outcome measures every 6 months over 2.5 years of follow-up.

A substudy will be conducted on the relationship of the psychosocial predictors with immune markers for CIN progression (CD4+ lymphocyte and activated, cytotoxic CD8+ lymphocyte percentages) and the relation of those markers to distress. The control variables are 1) biological, sociodemographic, and lifestyle more specifically related to CIN (e.g., HPV type, self-care [frequency of prior Pap smears], smoking, sexual habits, oral contraceptive use, history of HSV-2 infection, history of other sexually transmitted diseases); 2) control variables more specifically related to immune measures (sleep deprivation, exercise frequency, diet, alcohol use, caffeine intake, use of prescribed medications known to affect immune measures and recreational drug use); and 3) internal validity checks (i.e., distress in reaction to the abnormal Pap smear, and suspicion about having invasive cervical cancer at enrollment).

The findings of this prospective study may have great relevance for the development of behavioral interventions to prevent the initial development and recurrence of CIN. Such work would be evaluated in conjunction with 1) gynecologic oncology treatment of CIN lesions, 2) potential vaccines using adoptive transfer of cytotoxic T lymphocytes (Melief 1992), as well as antiviral therapies for HPV now in development (Phelps and Alexander 1995), and 3) Pap smear screening programs. Such interventions may be especially important for HIV-1-infected women who are coinfected with high-risk HPV types, because they are at increased risk for clinically significant immunosuppression and more rapid progression of CIN (Goodkin et al. 1993c).

Conclusion

Further studies to establish the potential influence of psychosocial factors on CIN progression are warranted (Goodkin et al. 1993a, 1993b, 1993c, 1993d). One reason that we have focused here on the early stages of disease progression is that immunologic defense

processes may have a more important role at those stages, with such processes having a stronger impact than in later disease stages, when the immunologic defenses may be assumed to have been largely overcome. The aforementioned Dutch study under way uses a prospective design with adequate attention to control variables—not only those known to be associated with CIN or cervical cancer (Goodkin et al. 1993a, 1993b) but also those specific to immunologic effects (Kiecolt-Glaser and Glaser 1988).

Insight into the possible role of psychosocial factors in determining the course of CIN may contribute to the development of preventive strategies for cervical cancer—a disease that is, theoretically, 100% preventable. Yet, each year 420,000 new cases of cervical cancer are reported worldwide (Larsen et al. 1988). Moreover, an upturn in rates of mild and moderate CIN associated with epidemics of sexually transmitted diseases, specifically cervical HPV infection and HIV-1 infection, has led some to forecast a grim change in the future epidemiologic pattern of CIN. Results of new studies like the Dutch research described here could stimulate the development of behavioral interventions that, in conjunction with optimal Pap smear screening, standard gynecologic oncology follow-up care, and vaccines and medications now under development, are capable of reducing the risk for the initial development of CIN as well as the likelihood of recurrence of CIN in women who have previously received treatment. Such behavioral interventions could play an important adjuvant role, together with medically indicated gynecologic care, to maximize the cost-effectiveness of therapeutic interventions currently provided in the continued attempt to minimize the morbidity and mortality from this lethal, yet preventable, disease.

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Chapter 4

Neoadjuvant Immunostimulation in Oncologic Surgery

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In the early 1970s, Burnet (1970) formulated his pioneering immunosurveillance theory: Most malignantly transformed cells are immunogenic and are probably destroyed by an effective host defense; only tumor cells escaping destruction may give rise to a manifest tumor. In contrast to Burnet's model, initial enthusiasm for tumor immunology was dampened by subsequent findings that many tumors are only poorly immunogenic or completely nonimmunogenic. Nevertheless, the effect of immunotherapy on progression of metastatic cancer was investigated, and many successful remissions were reported (Rosenberg et al. 1987; Silver et al. 1987; Topalian et al. 1988). More recently, perioperative immunostimulation (e.g., use of interleukins and interferons) has been recognized as an opportunity to reduce postoperative immunosuppression.

Surgery has been associated with activation of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis resulting in increased secretion of adrenocorticotropic hormone (ACTH) and cortisol (Fishman et al. 1993). It has been suggested that this is one of the possible pathways along which the effect of surgical stress on immune function is mediated. In addition, numerous psychoneuroimmunology studies have shown that psychological distress states and affective disorders may be accompanied by increased secretion of glucocorticoids, which have been shown to suppress immune function. Thus, aside from neuroendocrine dysregulation

and concomitant immunosuppression due to surgery, heightened levels of psychological distress that cancer patients frequently experience 1 to 2 years postoperatively also can impair immune function. It has been suggested that psychosocial intervention administered before and immediately after surgery may not only improve coping abilities and reduce psychological distress but also deter impairments in immune function (Fawzy et al. 1990a, 1990b). Therefore, psychotherapy may be an important modality as an adjunct to regular medical treatment.

The central question of this chapter is, What can be done to prevent immunosuppression in the period prior to surgery and thereafter to decrease the risk of metastasis? This chapter addresses this question by describing the influences of surgical stress and related factors (anesthesia, blood transfusion, and psychological distress) on immune function. The effects of exogenous administration of immunostimulants are reviewed. The chapter ends with a discussion of the effects of psychosocial intervention on immune function. Before addressing these issues, I present a short review of the role of both cell-mediated and natural immunity in the host response to tumor cells.

Relationships Between Immune Function and Tumor Growth

Inhibition of Tumor Growth

An increasing body of experimental data indicates that the inhibition of tumor growth is under the control of both T cell–mediated immunity and nonspecific immunity (natural killer [NK] cells and macrophages) (Herberman 1984). T cell–mediated immunity is primarily relevant for the control of the growth of tumors expressing specific antigens (Melief and Kast 1990, 1991). A tumor is considered immunogenic when it presents processed antigen as peptide bound to major histocompatibility complex (MHC) class I or class II molecules. Studies with animal models have shown that tumors induced by viruses (e.g., Epstein-Barr virus, human

papillomavirus [HPV]) are most likely to be immunogenic. Other, chemically induced tumors (e.g., lung cancer) appear to be poorly immunogenic or nonimmunogenic. Until recently, it was assumed that most (spontaneous) human tumors express insufficient levels of antigenic determinants. However, recent observations suggest that spontaneous cancers display a broad spectrum of immunogenicities and that therefore the assumption that spontaneous cancers are always nonimmunogenic requires revisiting (Brasseur et al. 1992; Heike et al. 1994).

It has been suggested that tumors are also immunosurveyed by NK cells (Herberman et al. 1987; Melief 1992). These immune cells are capable of recognizing and eliminating tumor cells without prior antigen priming or MHC restrictions (Ljunggren and Kärre 1990). Moreover, NK cells seem to be more effective in dealing with a small number of tumor cells than in dealing with a large tumor cell load (Herberman 1989; Herberman et al. 1987). Evidence in experimental animal models has suggested that NK cells are important in host defense against circulating tumor cells and can prevent the development of tumor cells into micrometastases (Herberman 1989; Melief and Kast 1991). Unlike cytotoxic T lymphocytes, NK cells are in many cases less commonly detected among tumor infiltrating lymphocytes (Van Ravenswaay et al. 1992). The distribution of cytotoxic T lymphocytes and NK cells among tumor infiltrating lymphocytes varies significantly by the type of tumor.

Certain cytokines (e.g., interleukin-2 [IL-2], interferon-γ, interleukin-12 [IL-12]) that are produced by activated T helper (CD4+) lymphocytes potentiate the activity of NK cells (Redondo et al. 1986). In addition to its important immunomodulating property, IL-2 also influences wound healing. That is, the inflammatory response, involving collagenase activity together with microvascular and fibroblast proliferation, is under the regulatory control of a number of cytokines.

Immunologic Escape

Most cancer patients have an intact immune system at the time of the initial diagnosis. Therefore, tumor cells must have ways to es-

cape eradication by the immune system. Several mechanisms have thus far been identified.

1. *Immunoselection.* Experimental data clearly indicate that a tumor is a heterogeneous population of malignant cells composed of a series of related but genotypically distinct individual clones (Melief and Kast 1991). Genetic clonal heterogeneity of tumor cell populations is the basis of their heterogeneity in many phenotypic characteristics such as degree of malignancy, invasiveness, and metastatic ability, and their antigenic and immunogenic properties. Based on animal studies, it has been proposed that during tumor growth, immune responses are evoked against each clone and are directed against primarily the most immunogenic clones. As a result of an effective immune response, these immunogenic clones could be eliminated or suppressed, whereas other (nonimmunogenic) clones would be undamaged and have the opportunity to expand (Heike et al. 1994).
2. *Changes in expression of MHC class I antigens.* Changes in expression of MHC class I antigens may occur, particularly in those cancer cells in which tumor-specific antigen cannot be lost (e.g., SV40-transformed cells), since expression is required for the maintenance of the malignant phenotype (Herberman et al. 1987). Down-regulation of MHC class I antigen expression can allow escape from cytotoxic T lymphocyte–mediated immune surveillance; however, the effects of such down-regulation appear to be tumor-specific (Schreiber 1993). In addition, loss of the antigenicity of the target molecule, rather than loss of its expression, may sometimes be the mechanism of escape.
3. *Suppression of cytotoxic action of CD8+ T cells.* The cytotoxic action of CD8+ T cells has been found to be suppressed by soluble immune complexes ("blocking factors") and "suppressor cells," the latter of which are usually signaled by cytokines produced by CD4+ cells (Awwad and North 1990).
4. *Local evasion.* Malignantly transformed cells secrete the cytokine transforming growth factor–β (TGF-β), which is known to inhibit IL-2-dependent proliferation of T lymphocytes and the

induction of cytotoxic T lymphocytes in mixed lymphocyte cultures (Heike et al. 1994; Wahl et al. 1989).

Influences of Surgery and Related Medical Interventions on Immune Function

Surgery

It has been suggested that surgery can alter the immune response. The results of several studies have shown that surgery may significantly decrease NK cell cytotoxicity and lymphocyte proliferative response in patients in the early stages of cancer (stages I and II) relative to their preoperative levels (Lennard et al. 1985; Pollock et al. 1992; Uchida et al. 1982). This decline becomes manifest within a few hours and returns to preoperative levels within 3 weeks. An important finding is that the preoperative levels of these cancer patients did not differ from those of healthy donors (Pollock et al. 1992). These surgery-related immune impairments need to be differentiated from perioperative anesthetic-induced influences, which generally last only approximately 24 hours postoperation.

The extent of the operation seems to determine the level of immune impairment. In patients undergoing a minor operation, less impairment was observed (Lennard et al. 1985). On the first postoperative day, the absolute lymphocyte count of patients who underwent minor surgery declined. By the third postoperative day, their CD4 cell counts had declined. In contrast, in patients who had undergone major surgery, all lymphocyte subset counts (except for B cell counts) were already significantly decreased on the first postoperative day. After seven days, the lymphocyte phenotype counts of both groups had returned to near preoperative values and remained so through day 21 (Lennard et al. 1985). In addition, surgery has been associated with decreased IL-2 production, which has been suggested to be one of the mechanisms by which surgery impairs NK cell cytotoxicity (Kikuchi et al. 1988).

The mechanisms by which these immune changes are mediated have not yet been clearly identified, though there are some relevant preliminary findings.

1. *Histamine-induced paralysis.* The peripheral blood mononuclear cells (PBMNCs) of postoperative cancer patients include cytotoxic cells (cytotoxic T lymphocytes and NK cells), but the function of these cells is blocked by suppressor cells. A growing body of evidence implicates suppressor T cells expressing histamine$_2$ (H_2) receptors. These cells, in particular, may play an important immunoregulatory role in the production of a normal immune response. In one study, the postoperative NK cell cytotoxicity of cancer patients was blocked by these cells, whereas T cell function was not affected (Kikuchi et al. 1986). In addition, postoperative NK cell cytotoxicity decrements also seem to be mediated by monocytes, which are called *macrophages* on migration from the circulatory system into tissues. In fact, in vitro culture in the absence of suppressor monocytes revealed a recovery of lytic function after 24 hours (Uchida et al. 1982).
2. *Defects in calcium-dependent programming for lysis.* A study involving patients with sarcomas and other solid tumors demonstrated a significant decrement of NKCC within 18 hours after the operation. Specifically, it appeared that the rate of lytic programming was impaired, whereas tumor binding and recycling capacity after tumor lysis were intact. This finding suggests that the surgically induced NK cell defects might occur during the phase of the lytic cycle that involves intermediate calcium-dependent programming (Pollock et al. 1992).
3. *Endocrine modulation.* Surgical stress has been associated with the activation of the LHPA axis, which results in increased output of ACTH and cortisol usually detectable in the peripheral blood of patients 2 days postoperation (Fishman et al. 1993). These levels apparently returned to normal after 14 days in patients who underwent curative resection for malignant disease of the gastrointestinal tract. Increased levels of these hormones have been associated with immunosuppression, including decreased lymphocyte proliferation and NK cell cytotoxicity both in vitro and in vivo (Van den Brink et al. 1992). Mastectomy has been associated with increased serum prolactin, which remains at a high level over a period of 3 months (Barni et al. 1987;

Wang et al. 1986). High levels of prolactin may directly stimulate tumor growth. The complete role played by endocrines (e.g., estrogens and prolactin) in human tumors (e.g., breast cancer) has not yet been clarified, although some animal studies strongly suggest stimulatory effects on tumor growth (Bulbrook et al. 1988).

In addition, a moderate level of prolactin has been demonstrated to be essential for optimal immune functioning (e.g., proliferation of T lymphocytes in response to IL-2) (Clevenger et al. 1991). However, chronically elevated prolactin levels may reduce the number of NK cells and inhibit their function (Nicoletti et al. 1989). Thus, while it can be assumed that surgical stress may stimulate micrometastases either directly by endocrine dysregulation (in the case of breast cancer) or indirectly via immunosuppression, the precise mechanisms remain unknown.

In summary, surgery is characterized by acute hormonal and metabolic changes that are accompanied by decreases in cellular immune functions, including NK cell cytotoxicity and cytotoxic T lymphocyte activity. In addition, changes in cytokine levels stimulating these functions (e.g., IL-2) also have been described during the perioperative period. All of these physiological stress responses are imposed on a host concomitantly burdened with temporary anesthetic-induced immune impairment.

Blood Transfusion

Other factors, aside from surgery, seem to influence immune function. Several clinical studies have demonstrated that perioperative blood transfusions in patients undergoing major surgery (e.g., mastectomy or colorectal resection) induce immunosuppression. The immunologic changes observed after blood transfusion include decreased CD4 (T helper)/CD8 (T suppressor) ratio, NK cell cytotoxicity, and IL-2 production (Schriemer et al. 1988). In order to avert the potential immunosuppressive effects of transfusion with allogeneic blood (e.g., by transmission of viral particles and bacteria), transfusion with autologous blood has been suggested. Until

recently, the results of several studies have shown that the prognosis is the same both for recipients of autologous blood and for those transfused with allogeneic blood (Busch et al. 1993). In contrast, leukocytes have been suggested to mediate transfusion-induced immunosuppressive effects. In patients undergoing elective colorectal surgery, transfusions with leukocyte-depleted blood resulted in significantly less NK cell cytotoxicity decrements than whole-blood transfusions (Jensen et al. 1992). In contrast, buffy coat–depleted blood (which contains fewer leukocytes than does whole blood) seems to engender larger detrimental immune effects (Houbiers et al. 1994). In a randomized clinical trial in which patients were assigned to a leukocyte-depleted blood group, buffy coat–depleted blood group, or a nontransfusion group, there were no differences in survival among subjects receiving each of the transfusion regimens. Patients who received a transfusion of any sort had a lower 3-year survival than nontransfused patients (Houbiers et al. 1994). The degree to which these survival differences are related to immune changes observed during each regimen should be examined in future studies.

Adjuvant Chemotherapy and Radiotherapy

After a curative resection, there is a higher risk of metastasis among patients with larger tumor mass and local regional dissemination evaluated by lymph node biopsy. Often, in such cases, adjuvant chemotherapy, in combination with radiotherapy, is offered in order to kill residual tumor cells. Studies have shown that these regimens may alter the balance of host responses (Brenner and Margolese 1991). For instance, NK cell cytotoxicity in breast cancer patients declined as a result of chemotherapy (Brenner and Margolese 1991). In patients who received chemotherapy in combination with local radiotherapy, compared with those patients receiving radiotherapy alone, the decline in NK cell cytotoxicity was still present 12 to 18 months later (Tichatschek et al. 1988). In the patients who received radiotherapy alone, there was a trend toward an increased percentage of total T lymphocytes, whereas in the patients receiving both local irradiation and chemotherapy, the

percentage of T lymphocytes did not change (Tichatschek et al. 1988).

Clinical Relevance of Surgical and Related Influences on Immune Function

Infectious complications after surgery may be mediated by alterations in the host response to surgical stress. Cancer patients whose lymphocyte proliferative responses to phytohemagglutinin declined by more than 30% of their baseline values 5 to 7 days after surgery were very likely to develop infectious complications (Faist et al. 1986). Thus, alterations in T cell function seem to precede the development of postoperative infectious complications in critically ill surgical patients. The incidence of postoperative sepsis and mortality appeared to be higher among those with evidence of protein-energy malnutrition (Chandra 1983a). In addition, several findings confirm changes in immunocompetence in protein-energy malnutrition (such as cutaneous anergy) (Chandra 1980, 1983b; Chandra and Newberne 1977; Gross and Newberne 1980). Measurement of protein-energy malnutrition can be achieved with minimal patient burden as well as high reliability and validity with the Protein-Energy Malnutrition Scale (Linn 1984).

The risk of development of distant metastases may be increased by "spilling over" of tumor cells into the blood and lymphatic circulatory system as a result of surgical manipulation and subsequent immunosuppression. However, the relation between the immunologic changes and clinical outcome after surgery is still unproven (Lennard et al. 1985).

Neoadjuvant Immunostimulation

There exists a growing body of evidence that immunotherapies, including IL-2 and interferons, may reduce immunosuppression due to surgery. Pharmacotherapy that inactivates suppressor (CD8+) T lymphocytes (H_2 receptor antagonists such as ranitidine) and antiestrogens are also included under this rubric.

Exogenous Immunostimulants

Since IL-2 is known to potentiate NK cell cytotoxicity, exogenous administration of IL-2 has been identified as one of the possible avenues for buffering surgery-related NK cell cytotoxicity decrements. Studies with animals and humans have suggested that perioperative therapy with IL-2 may help in alleviating such deficits.

In animal models, IL-2 has been demonstrated to be an effective adjuvant to surgery. In mice, a rapid increase in NK cell cytotoxicity was observed after administration of IL-2 (Henney et al. 1981). Moreover, perioperative IL-2 administration enhanced survival following resection of a locally invasive murine fibrosarcoma in mice (Dubinett et al. 1993). It has also been demonstrated that local perioperative IL-2 administration augments the number of wound-infiltrating lymphocytes in mice and therefore may increase the ability of these lymphocytes to reach sites of residual tumor (Dubinett et al. 1993).

Perioperative administration of IL-2 in patients with colorectal carcinoma resulted in a significant increase in T lymphocyte and NK cell numbers, compared with preoperative levels, when these measures were monitored for 14 days after the operation (Brivio et al. 1993a). In addition, histological examination showed significant infiltration of lymphocytes into the tumor tissue in 14 of the 16 subjects (Brivio et al. 1993a). Lymphocytic infiltration of tumor tissue has often been associated with a favorable prognosis (e.g., in patients with malignant melanoma) (Griffith et al. 1990). However, it is still unproven that such infiltration results in improved survival. Likewise, treatment with IL-2 prevented the postoperative decline in NK cell cytotoxicity that was clearly demonstrated in patients undergoing surgery for colorectal carcinoma (Nichols et al. 1992). A similar result was obtained among gastric or colorectal cancer patients who received a low dose of interferon perioperatively; however, the interferon did not prevent postoperative impairment of IL-2 production (Sedman et al. 1988). In a randomized trial to determine the effect of dose strategy for interferon-α with advanced breast or ovarian cancer patients, patients receiving a high dose demonstrated improvements in immune measures (increased

number of CD4 cells and NK cell cytotoxicity) and survived longer than patients who received a low dose (Silver et al. 1987). Other cytokines, such as interferon-γ and IL-12 (originally described as "NK cell stimulatory factor"), may prove helpful in this setting as well (Jenks 1996).

Pharmacologic Therapy Inactivating Suppressor (CD8+) Lymphocytes

An alternative to exogenous immunotherapy might be the selective pharmacological inactivation of host suppressor cells. For reasons mentioned earlier in this chapter, the suppressor cell presenting H_2 receptors might be an important target for pharmacologic manipulation (Osband et al. 1986). Cimetidine, which is a specific H_2 receptor antagonist, significantly slowed metastatic development and prolonged survival in tumor-bearing mice (Lewis lung carcinoma) in association with decreased activation of suppressor cells (Osband et al. 1986). Cimetidine also seems to augment NK cell cytotoxicity both in vitro and in vivo (Hellstrand and Hermodsson 1987; Kikuchi et al. 1986). Cimetidine augmented the NK cell cytotoxicity in ovarian cancer patients with no residual tumor but not in healthy women. Particularly, patients with low baseline NK cell status before treatment showed marked enhancement (Kikuchi et al. 1986). In addition, this drug seems to have a significant protective effect in adjuvant chemotherapy with respect to inhibition of IL-2 production (Kikuchi et al. 1988). Cimetidine is associated with a number of drug interactions and several (particularly antiandrogenic) toxic side effects. Hence, studies of the more recently developed H_2 receptor antagonists (ranitidine and famotidine) with fewer drug-drug interactions and toxic side effects may be justified (American Medical Association 1992).

On the basis of current knowledge of H_2 receptor antagonists and their inhibition of suppressor CD8+ T lymphocytes, this type of treatment appears to be preferable to treatment with levamisole, a nonspecific immunostimulator augmenting both lymphocyte effector and suppressor cells (Redondo et al. 1986). In vitro,

levamisole enhanced T cell proliferation and the inducing activity of IL-2. However, in a randomized trial of levamisole versus placebo as an adjuvant therapy in malignant melanoma patients, the treatment and control groups did not differ in terms of disease-free interval, time to appearance of visceral metastases, and survival—a finding which suggests that more specific immunotherapies are needed (Spitler 1991).

Endocrine Treatment

The timing of surgery for tumor reduction in relation to day of the menstrual cycle may have effects on postoperative mortality. This has been demonstrated in animal studies by examining frequency of micrometastasis (Ben-Eliyahu et al. 1994) and has been associated with decreased NK cell cytotoxicity per NK cell (Ben-Eliyahu et al. 1996). Further, the data of this group of investigators suggest that despite a transitory increase in the number of NK cells in blood by β-adrenergic agonists, the in vivo effect suppresses NK cell cytotoxicity in the rat (Ben-Eliyahu and Shakhar 1998). This suggests a therapeutic potential for β-blockers. In addition, this finding might have clinical relevance for survival in humans (Goodkin et al. 1995). Hence, endocrine treatment may have a role as a neoadjuvant strategy.

Endocrine treatment (e.g., with tamoxifen, an estrogen receptor blocker) is effective in patients with breast cancer (more specifically in those with estrogen receptor–positive tumors) as an adjuvant, including in cases of metastatic disease (Baum et al. 1992). In addition, tamoxifen has the ability to modulate human NK cell cytotoxicity. Stage I postmenopausal breast cancer patients ($N = 18$) receiving tamoxifen (for 8 weeks) showed an increase in NK cell cytotoxicity relative to their pretreatment levels (Berry et al. 1987). Both animal and human studies suggest the possibility that estrogens can inhibit NK cell cytotoxicity (Van der Pompe et al. 1994b). Contrary to expectations, this NK cell cytotoxicity enhancement was mediated not by reduced estrogen levels but by a reduction in prostaglandin production (Berry et al. 1987). Reduction of immunosuppression might explain the observation that

breast cancer patients (those with stages I and II) receiving tamoxifen in addition to perioperative chemotherapy had survived longer than those receiving chemotherapy alone (Toi et al. 1992). Moreover, whereas perioperative chemotherapy alone did not result in a significant survival advantage, adjuvant tamoxifen demonstrated a significant improvement in disease-free survival over a 10-year follow-up period in one study (Berry et al. 1987).

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In conclusion, perioperative treatment with immunotherapy (IL-2 and interferons) appears to reduce or prevent immunosuppression induced by surgery, blood transfusion, and anesthesia. This immunoenhancement may positively affect the prognosis for cancer patients, as has been demonstrated in animal models. Whether immunotherapy results in a survival improvement in humans remains to be elucidated. Likewise, the results of studies on the effect of pharmacologic manipulation (H_2 receptor antagonists, levamisole, and tamoxifen) point to immunologic changes, including increases in NK cell cytotoxicity and T cell function. Whether these immune improvements result in a survival advantage, as has been observed in patients receiving tamoxifen, awaits testing on a larger scale.

Psychological Distress Due to Cancer Diagnosis and Surgery

Cancer patients may face serious psychological burdens after surgery, including high levels of anxiety and depressive symptoms and illness-related worries (Irvine et al. 1991; Morris et al. 1977; Plumb and Holland 1977). Those facing such psychological burdens may manifest with psychopathology as well—most frequently adjustment disorders, but also, and not infrequently, major depressive disorder. In physically healthy subjects, psychological distress states and affective disorders have been associated with LHPA hyperactivation, which results in increased secretion of

ACTH and cortisol (Brambilla et al. 1986; Kitamura et al. 1989; Rubin 1989; Von Bardeleben and Holsboer 1988). High levels of ACTH and cortisol are associated with decrements in immune function, including decreased proliferative responses of T lymphocytes and NK cell cytotoxicity (Herbert and Cohen 1993; Stein et al. 1991; Weisse 1992). Thus, psychological distress before and after surgery or adjuvant treatment may impose immune decrements on a patient concomitantly burdened with transient surgically induced immune impairment.

The psychological reactions of postoperative cancer patients are determined mainly by the perception of impending loss (the threat of a recurrence, disability, or death) and are comparable to those observed after major object loss (child or spouse); the latter have been observed to result in significant impairments in NK cell cytotoxicity and T cell mitogen responses (e.g., loss of breast) (Irwin et al. 1987a, 1987b). In contrast to the transient postoperative immune decrements discussed earlier, these bereavement-related decrements returned to baseline only after 4 to 14 months (Schleifer et al. 1983). This period parallels the time course of increased morbidity and mortality from a variety of illnesses in the year following a loss (Parkes and Weiss 1983). Likewise, the high levels of anxiety that a considerable number of cancer patients still experience 1 to 2 years after surgery may influence disease progression. A few studies have shown that high levels of psychological distress, specifically when this distress is accompanied by feelings of hopelessness and despair, result in a survival disadvantage (Greer et al. 1979, 1990). However, it still remains to be demonstrated whether these survival differences are correlated with immunologic alterations.

Whether a patient after a period of grief and mourning (e.g., 4 months), observed in most surgical cancer patients, regains emotional stability depends partly on their psychological resiliency. It has been widely accepted that patients who make use of adaptive coping strategies (active coping, expression of anger, and active seeking of instrumental and emotional social support) when facing negative life experiences are less likely to face psychological distress and develop affective disorders than are patients who make

use of maladaptive coping strategies (denial, passivity, helplessness, and withdrawal and behavioral and mental disengagement). The results of several studies have shown that adaptive coping styles are associated with lower activity of the neuroendocrine system and increments in immune measures compared with maladaptive coping styles, as summarized by Goodkin and colleagues (1993).

In addition, some studies have shown that cancer patients who express negative affect and anxiety have an improved prognosis. Derogatis and colleagues (1979) showed that long-term survivors had higher levels of anxiety, depression, and alienation at the time of the initial diagnosis than did patients who died within 1 year of diagnosis. One explanation might be that patients who lived longer may have been better able to communicate their feelings. Thus, it can be assumed that psychological distress levels, which are increased by use of maladaptive coping strategies, may be accompanied by immunosuppression. Therefore, psychotherapy may be an important modality complementing the medical treatment of patients with cancer. However, it should also be noted that traumatic distress appears to differ from general dysphoria in that the former may be associated with increased immune measures, such as elevated NK cell cytotoxicity in combat veterans with long-term posttraumatic stress disorder (Laudenslager et al. 1998). Hence, relationships between psychological distress and immunity may be more complex than originally thought.

Effect of Psychosocial Intervention on Psychological and Immune Function

The results of several studies have shown that provision of psychosocial intervention as well as patient education can improve coping abilities and reduce psychological distress of cancer patients in different stages of their disease (Alcoe and Gilbey 1996; Andersen 1992; Trijsburg et al. 1992; Visser and Goodkin 1996). The assumption that psychosocial intervention reduces the activity of the neuroendocrine system challenged several investigators to evaluate the effect of psychosocial intervention on endocrine and

immune function. To date, only a few cancer-focused psychosocial intervention programs have been evaluated for such physiological effects (Fawzy et al. 1990a, 1990b; Levy 1990). Two commonly evaluated psychological intervention techniques in studies on intervention-related immunologic changes are progressive muscular relaxation training and guided imagery. These techniques have been most extensively evaluated with healthy adults.

Psychosocial Intervention and Immune Function in Healthy Subjects

In healthy adults, increases in NK cell cytotoxicity, T cell proliferative responses to mitogens, and phagocytic functioning of neutrophils have been found after relaxation training (Kiecolt-Glaser et al. 1986; McGrady et al. 1992; Peavey et al. 1985) and guided imagery in conjunction with relaxation training (Hall et al. 1992). Decreases in herpes simplex virus (HSV) type 1 or 2 antibody titers—which are salutary and reflect decreased viral reactivation from the latent state—were also observed in healthy geriatric patients receiving relaxation training compared with those assigned to either a no-treatment control group or to a social contact group (Kiecolt-Glaser et al. 1985). In addition to these immunologic changes, most studies reported less anxiety and more adaptive coping responses among intervention subjects (Kiecolt-Glaser et al. 1985; Peavey et al. 1985). These findings support the assumption that lower levels of psychological distress may be accompanied by immune enhancement. It should be noted, however, that these were short-term interventions and that no clinical health benefits were examined.

In contrast to the findings of immunoenhancing effects after relaxation training in the aforementioned studies, results from a subsequent study showed diminished lymphocyte proliferative responses postintervention in patients assigned to a guided imagery group and those assigned to a relaxation group compared with responses in patients in a no-treatment control group, which did not change (Zachariae et al. 1994). Likewise, decreases in NK cell cytotoxicity were observed immediately after the intervention,

with a return to preintervention levels 1 hour later. These changes can be explained by the stress induced by the experimental condition (e.g., by venipuncture directly after the intervention) (Zachariae et al. 1994).

Overall, the results of several studies suggest that relaxation training and guided imagery enhance cellular immune function in healthy adult subjects. However, these results need to be interpreted with some caution because of the limited sample sizes in these studies.

Psychosocial Intervention and Immune Function in Cancer Patients

In a pilot study, Gruber and colleagues (1988) evaluated the efficacy of a guided imagery plus relaxation training program of 1 year in a mixed group of cancer patients with metastatic disease (Gruber et al. 1988). The authors noted increases in several immune measures, including lymphocyte proliferative responses to phytohemagglutinin and concanavalin A, NK cell cytotoxicity, IL-2, and IgG levels, relative to baseline. Other research groups (Fawzy et al. 1990a, 1990b; Levy 1990) evaluated the effect of cancer-focused psychosocial intervention programs on immune function in postoperative cancer patients. Levy (1990) evaluated psychosocial and immunologic changes in a randomized trial with colon cancer and malignant melanoma patients. Compared with patients in the no-treatment control condition, patients receiving an individually administered cognitive-behavioral therapy showed an increase in NK cell count and a trend toward higher NK cell cytotoxicity. A similar pattern emerged in a randomized prospective study involving postoperative patients with malignant melanoma who were assigned to either a 6-week structured psychiatric group intervention or a standard medical care control condition (Fawzy et al. 1990a, 1990b).

In all three studies (Fawzy et al. 1990a, 1990b; Gruber et al. 1988; Levy 1990), the pattern of psychological changes paralleled the changes in the immune measures. That is, decrements in distress and increases in active coping and survival were accompanied by

increments in NK cell count and activity. These observations demonstrate the possibility that psychosocial intervention can positively affect immunologic processes in cancer patients. However, it is important to determine whether these immunologic effects have any impact on tumor growth.

Spiegel and colleagues (1989) found that patients with metastatic breast cancer who were assigned to a 1-year group psychotherapy condition had a significantly longer survival time—nearly twice as long—than those who received standard oncologic care only. In view of these findings, the authors postulated an increase in immune function accompanying reductions in psychological distress as one of the explanatory hypotheses for the effect of this intervention on survival. This hypothesis may be plausible to the extent that the intervention significantly reduced psychological distress. Such reduction in psychological distress may have, in turn, reduced levels of LHPA neuroendocrines (cortisol and ACTH)—which may suppress cellular immune function—and, ultimately, affected the course of the tumor.

Davis (1986) evaluated the effects of biofeedback and cognitive therapy administered to a sample of 25 postoperative breast cancer patients over a period of 8 weeks. The most salient finding of this study was that 24-hour cortisol levels among the 12 treated patients were reduced relative to those of the control patients. However, this study did not examine immunologic or health effects.

More recently, Fawzy and colleagues (1993) showed that postoperative melanoma patients receiving a psychosocial intervention, compared with those who received surgery alone, had a significantly improved survival time at 5 to 6 years follow-up. (This finding, however, was unrelated to the increases in NK cell counts and activity reported earlier in this subsection.)

A human gene (*MAGE-1*) directing the expression of a potential tumor rejection antigen in malignant melanoma tissue has been identified (Van der Bruggen et al. 1991). This implies that T cell–mediated immunity is likely to be significantly involved in the control of tumor growth.

In addition to the thickness of the skin lesion, the density of tumor infiltrating lymphocytes in the primary tumor and the mitotic

rate are important prognostic factors in malignant melanoma (Karjalainen et al. 1992). To our knowledge, these two factors have not been incorporated into Fawzy et al.'s study design. Therefore, the nature of the relationship between intervention-associated immune function changes, on the one hand, and the course of malignant melanoma, on the other, warrants further investigation.

Conclusion

The central question of this review is, What can be done to prevent immunosuppression in the period prior to surgery and thereafter to decrease the risk of residual tumor cell spread? As described in this review, surgery-induced immunosuppression can be reduced by different measures, including minimization of surgical trauma, hyperalimentation, avoidance of general anesthesia, and avoidance of transfusion with whole blood. Because the immunosuppressive effects of surgery cannot be eliminated totally, exogenous immunostimulation should be considered. Interleukin-2 and interleukin-12, interferons, and pharmacologic therapy with levamisole or H_2 receptor blockers to inactivate suppressor cells are examples of such immunostimulation. In the case of breast cancer, tamoxifen, a commonly used endocrine treatment, appears to protect the immune system against immunologic insults by chemotherapeutic agents. Likewise, provision of psychosocial interventions can reduce psychological distress and possibly prevent immunosuppression, improving postoperative functional recovery as well as decreasing complications and length of hospital stays.

On the basis of the specific psychological reactions to a cancer diagnosis, we developed a framework for psychotherapy with postoperative cancer patients. This model has been described in detail elsewhere (Van der Pompe et al. 1994a) in the context of treatment of breast cancer patients. The model has three main foci:

1. *Facilitation of grief work.* During the first few months after the operation, the therapy focuses on working through the existential crisis provoked by the confrontation with a potentially

life-threatening illness. In this phase of the therapy, patients are encouraged to express their feelings of anger and fear toward their cancer. In addition, relaxation training exercises are offered to reduce anxiety resulting from the cancer diagnosis or from adjuvant radiotherapy and chemotherapy.

2. *Rehabilitation of coping abilities.* After facing the emotional crisis of the first few months after diagnosis and surgery, patients may become more open to experiences and exercises that may improve their coping abilities. This point can be reached by discussing and practicing personally effective coping strategies and reframing rigid and distorted cognitive appraisals.
3. *Provision of social support.* Although this program can be administered on an individual basis, the supportive environment created in group psychotherapy can provide additional psychotherapeutic benefits. Patients can share their mutual experiences with respect to the diagnosis and treatment of cancer and can use the group to obtain peer support and emotional encouragement from others undergoing similar difficulties.

The foci in this model were developed with respect to patients with breast cancer. Although it might be expected that these foci would also apply to interventions with patients with other tumors (e.g., malignant melanoma and colorectal carcinoma), it should be cautioned that the results from this program, like the results from some of the studies summarized in this chapter, may prove to be cancer-specific; therefore, similar studies should be done across a variety of tumor types to establish the potential generalizability of the intervention. Finally, it should be noted that psychosocial interventions are not proposed as an alternative or as an independent treatment for cancer, but as an adjunct to medical treatment—that is, a new type of adjuvant.

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Chapter 5

Psychoneuroimmune and Endocrine Effects on Cancer Progression

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Once believed to be autonomously functioning mechanisms, the nervous, endocrine, and immune systems are now known to be integrally connected, with exquisitely sensitive communications and interactions. The continual fluctuations in neuroendocrine-immune function are not exclusively regulated by the internal cellular environment. External stressors of varying degree and type (i.e., physical, environmental, and psychosocial) have also been found to exert a profound influence on neuroendocrine-immune function.

The effect of external stressors appears to be relatively nonspecific. The body, it seems, does not differentiate carefully between the various types of stressors in determining its response. The overlap of this physiological stressor response can be seen in an individual who has been diagnosed with a life-threatening disease such as cancer or AIDS. The disease itself is a stressor, as are the treatments the patient undergoes and the psychosocial changes that occur as a result of having both the disease and the treatments.

The body's lack of specificity in responding to stressors enables the patient to derive nonspecific physiological benefits from exter-

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nal psychosocial interventions. This is particularly important in the setting of chronic or terminal illness, in which psychosocial distress often responds well to intervention, whereas physical symptoms may not respond as well. A number of studies have indicated that moderate alterations in an individual's social or emotional burden can slow or reverse many of the stressor-related changes in neuroendocrine-immune axis function. Such an effect, in turn, appears to slow disease progression and prolong survival time, as well as improve quality of life.

In this chapter, we provide the reader with an introduction to the psychoneuroimmunologic mechanisms activated by stressors. We begin by briefly outlining the basis for current psychoneuroimmunologic theory. We then examine the impact of stressor-induced changes on the nervous, endocrine, and immune systems. Using life events as a model for acute and chronic life stressors, we review studies that have demonstrated the impact of psychological stressors on cancer progression. Finally, we explore the mechanisms of internal and external modulation of cancer progression, looking at internal styles of affect, personality, and coping and external factors of social support and emotional expression.

Mechanisms of Stressor-Induced Immunosuppression

The demonstration of the "mind-body" interaction at an investigative level has, until recently, been severely limited by restrictive analytic techniques. With in vitro assays, the common laboratory standard used to investigate these interactions, immune cells are removed from their natural neuroendocrine environment, and this makes assessment of psychophysiological interactions difficult, if not impossible. The basis for the elucidation of psychoneuroimmunologic mechanisms influencing disease progression is a series of findings that form a template for subsequent findings in the area of brain-body interaction. Among the general findings is the observation that stressors have an immunosuppressive effect that can be buffered by social support or emotional expression. The no-

tion that these modulators of external stress may alter the internal environment significantly enough to influence the in vivo progression of cancer rests on a series of premises that have varying degrees of supporting evidence.

1. Neural events influence the functioning of the immune system. Evidence for such an influence comes from the classic work of Ader and colleagues (1979), who demonstrated conditioned immunosuppression in animals.
2. Plausible, physiologic mechanisms that mediate the psychoneuroimmune effect can be identified.
3. Psychological, social, and neural effects on immune function can have clinically meaningful consequences as measured by altered susceptibility to infection or rates of cancer progression.

Physical stressors, such as aging, chronic infection and inflammation, cancer, surgery, malnutrition, as well as overtraining in athletes, have been shown to alter immune function (Dantzer and Kelley 1989; Fong et al. 1990; Goodwin et al. 1982; Irwin and Strausbaugh 1992; Naito et al. 1992; Sharp and Koutedakis 1992; Sternberg et al. 1992). Environmental stressors, such as noise, smoke, pollution, and alcohol, in humans suppress immune function, much as do acute foot-shocks, noise, and rotation in rats (Dantzer and Kelley 1989; Monjan 1984; Sieber et al. 1992; Sklar and Anisman 1979). Likewise, psychological stressors, such as the loss of a spouse, unemployment, marital discord, disruption of social support, anticipation of a cancer diagnosis, or caring for a loved one with Alzheimer's disease, have been demonstrated to adversely affect immunologic function (Arnetz et al. 1987; Eysenck 1988; Irwin et al. 1987; Kennedy et al. 1988; Kiecolt-Glaser et al. 1987a, 1987b; Schulz and Schulz 1992; Weisse et al. 1990).

Initially, the relationship between stressors and physical illness was felt to be mediated by endogenously released adrenocorticoids. However, work with intact and adrenalectomized rats later revealed a similar decrement in immune function independent of corticosterone levels (Keller et al. 1983). What has evolved during the years since those early studies is significant evidence of

a complex feedback loop between the immune system and the central nervous system (CNS) operating via the limbic-hypothalamic-pituitary-adrenal (LHPA) axis. This exquisitely sensitive system appears to be mediated principally by cytokines and modulated by neuroendocrine hormones, corticosteroids, catecholamines, and endogenous opioids (Dantzer and Kelley 1989; Meyerhoff et al. 1990; Sternberg et al. 1992). Recent evidence has demonstrated a variety of mechanisms by which these systems may influence one another. It has been shown, for example, that the spleen is heavily innervated and that norepinephrine and other neurohormones, such as β-endorphin, influence cell adhesion molecules on lymphocytes (Felten and Olschowka 1987). This peripheral communication between neurons and neurotransmitter receptors on lymphocytes allows for regulation of lymphocyte traffic and function.

At the same time, there are receptors in the CNS for cytokines, which have multiple effects on brain function. Different mechanisms of cytokine action in the CNS versus the peripheral immune system have been demonstrated, perhaps because of the great variation in cytokine form and function. For example, interleukins are synthesized peripherally by monocytes/macrophages and are also produced by glial cells and astrocytes in the CNS. Yet, many of the same substances have differing effects in vivo. For instance, interleukin-l (IL-1) administered peripherally stimulates immune function, whereas IL-1 administered centrally has the opposite effect, that of suppressing immune function (Irwin et al. 1990; Saperstein et al. 1992).

An alternative model for the effect of the nervous system on the immune system involves endocrine function. The brain regulates endocrine activity through the hypothalamus, which secretes a series of releasing factors that stimulate the release of peptide hormones such as adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and others from the pituitary. These, in turn, stimulate the release of target hormones, such as cortisol, estrogen, and progesterone, from target organs such as the adrenal gland and the gonads. Recent research suggests that one function of this neuroendocrine axis, particularly

the LHPA axis, is the regulation of immune function. For example, the action of IL-1 in the CNS as an immunosuppressant, referred to earlier, depends on the release of corticotropin-releasing hormone (CRH) from the hypothalamus (Irwin et al. 1990; Saperstein et al. 1992; Sapolsky et al. 1987).

The possible mechanisms for the association between stressors and immunosuppression are not mysterious. Stressors are associated with enhanced secretion of neurotransmitters such as norepinephrine that have been associated with sequestering of lymphocytes in lymphoid organs and suppression of lymphocyte function (Cross et al. 1987; Felten et al. 1991). In addition, stressors are associated with acute, and in some cases chronic, elevation of cortisol, an immunosuppressive adrenal hormone. Thus, stressor-induced immunosuppression could be mediated via neurotransmitters, hormones, or other pathways. Although much more remains to be elucidated, the notion of an independently operating immune system is no longer tenable.

Stressors and Cancer Progression

The influence of psychosocial stressors on the exacerbation of certain diseases is well established. The stimulant effects of stress on autonomic regulation is a possible mechanism in cardiovascular diseases such as essential hypertension, cardiac dysrhythmias, cardiomyopathies, and coronary artery disease (Jiang et al. 1993; Light et al. 1993; Shapiro et al. 1993). In a descriptive review of endocrine illnesses felt to be "stressor-induced," Coculescu (1989) included the diagnosis of "catecholamine cardiomyopathy," alluding to the prolonged elevation of catecholamines such as epinephrine and norepinephrine during chronic stressors and the resulting effect on heart muscle. Likewise, the connection between stressor and exacerbation of well-described immune disorders such as rheumatoid arthritis, inflammatory bowel disease, and asthma is also widely accepted by the medical community (Isselbacher et al. 1994). However, two areas of medical illness have, until recently, been believed to be relatively independent of psychosocial stress-

ors: cancer and infection. More recent studies have indicated that the cell-mediated and humoral immune processes involved in response to infection and in tumor progression may indeed be subject to psychosocial influences.

Role of Stressors in the Development of Infection and Cancer

Infection

The role of stressors in increasing susceptibility to infections has been demonstrated in both human and animal studies. Cohen and colleagues (1991) noted that subjects with a history of serious psychosocial stressors within the previous month were statistically more likely to get a cold when exposed to a controlled dose of rhinovirus than those with no such stress history. Similarly, Stone and colleagues (1992) found that subjects who developed colds after viral exposure had experienced a significantly higher number of major stressful life events in the prior year than those subjects who did not develop infection. Psychosocial stressors have been implicated in Epstein-Barr virus and herpes simplex virus infections regarding both reactivation of latent virus and increases in baseline antibody titers (Blondeau et al. 1993; Esterling et al. 1994; Glaser et al. 1991; Rand et al. 1990). Parasitic infections have also been studied: mice maintained in unstable social groups demonstrated stressor-induced immunosuppression (reduced levels of IgG), hypercortisolemia, and decreased clearance of parasites (Barnard et al. 1993). Administration of alprazolam to stressed mice resulted in a decrease in influenza A viral titers and in pulmonary vascular permeability (Freire-Garabal et al. 1993). Although stressors are clearly an influential factor in the development of infection, they are not the only factor that determines outcome. In a study examining exposure of healthy mice to acute *Toxoplasma gondii,* an immobilization stressor produced significant impairment in cell-mediated immunity; however, the degree of infection was also dependent on the timing of the stressor and the virulence of the infectious agent (Chao et al. 1990).

Cancer

Research investigating the connection between stressors and tumor progression has, until recently, focused on two of three possible interrelationships: 1) the impact of psychosocial stressors on disease progression and 2) the impact of psychosocial stressors on immunologic measures. The third relationship, that of the potentiation of tumor progression by immunosuppression, has largely been overlooked in psychosocial research because of methodological and interpretive dilemmas. One of the arguments frequently made against the plausibility of stressor-induced immunosuppression's potentiating cancer progression is that laboratory measurements of immunosuppression may not reflect clinically meaningful influences on disease course. For example, a decrease in lymphocyte natural killer (NK) cell activity in vitro does not necessarily correlate with an actual increase of tumor burden in vivo, since a number of other physiologic mechanisms are operating simultaneously within the body. This is an important concern, since the relevance of in vitro changes to in vivo illness is critical.

Similar mechanisms may, in fact, operate within the pathophysiology of infection and malignancy as a result of suppression of cell-mediated and humoral immune processes. Viral etiology is well reported in some, but certainly not all, cancers. One common model in which to study the relationship between immunosuppression and viral carcinogenesis is the development of malignancy after organ transplantation. The predominant posttransplant malignancies are squamous cell and connective tissue cancers and soft tissue/visceral sarcomas in which viruses such as human papillomavirus are often implicated (Penn 1994). In some malignancies, such as Kaposi's sarcoma and non-Hodgkin's lymphoma, cessation of immunosuppressants has been noted to result in neoplastic regression.

If immunosuppression is fundamental to tumor progression, why, then, is the incidence of posttransplant cancers relatively low, occurring in from 4% to 14% of survivors (Penn 1994)? One possibility includes the variety of etiologic agents and mediating mecha-

nisms other than viruses that contribute to the development of these tumors. For example, factors such as the transformation of oncogenes as a result of aggressive chemoradiotherapies, existence of preexisting dysplastic syndromes, and decreased clearance of toxins by overburdened host systems have been implicated in the etiology of malignancies in transplant patients. Second, the role of stressors in immunosuppression and tumor progression may be central in *promoting existing* tumor, rather than *initiating primary* carcinogenesis. This implication—that modulation of stressors affects disease progression—is supported by the current research involving psychosocial interventions in cancer patients. There are, however, no studies which suggest that stressor modulation prevents the development of cancer. This issue is likely to remain unresolved for now, though, because of the length of time necessary for tumors to become clinically detectable, a feature that makes the etiology difficult to pinpoint.

Immunologic Effects of Stressors on Cancer Progression

The relationship between various in vitro measures of immune function and cancer progression is a crucial issue. One important question concerns the degree of individual variation in immune susceptibility and response to stressor-induced perturbations. Bovbjerg and Valdimarsdottir (1993) studied women with family histories of cancer and noted that, independent of family history, women with greater emotional distress had lower NK cell activity, as did those with a family history of cancer. This suggests an intrinsic variability both in baseline immune sensitivity to stressors and in the ability of the immune system to recover from stressor-induced changes.

Does this type of sensitivity correspond to an increase in tumor incidence, progression, or virulence? In a series of studies, Levy and colleagues (1987, 1990, 1991) demonstrated an association between breast cancer progression, axillary lymph node status, and estrogen receptor status on the one hand and sustained psychosocial stressors and decreased NK cell activity on the other. A fur-

ther connection between preexisting host immunosuppression and increased cancer progression received support in an animal study by Sapolsky and Donnelly (1985), who showed that stressors were associated with a marked increase in injected tumor growth in lung, especially among older animals. Ben-Eliyahu and colleagues (1991) exposed disease-free rats to a stressor to significantly reduce their NK cell cytotoxicity levels and injected them with mammary (MADB-106) tumor cells. The rats were sacrificed, and the lung metastases were assessed 12 days later. The stressed, immunosuppressed rats demonstrated rapid metastatic spread of mammary tumor to lung in addition to increased plasma levels of cortisol and ACTH. In vivo β-adrenergic stimulation with metaproterenol suppressed blood NK activity in a dose-dependent manner and *reduced* resistance to tumor metastasis in the rat model (Shakhar and Ben-Eliyahu 1998).

These findings are not consistent with findings from several other studies. In a study of nonstressed, tumor-bearing mice, NK cell activity was elevated, not diminished, in preneoplastic mammary tissue and waned as spontaneous tumors developed (Wei and Heppner 1987). Enhancement of NK activity (by interleukin-2 [IL-2] or polyinosinic-polycytidylic acid) led to increased progression of dysplastic tissue to frank neoplasia. Suppression of NK cell activity led to longer tumor latency and slower progression, suggesting that a differential signal exists between normal and malignant tissue (Wei et al. 1989).

Thus, in animal and human studies, there is some evidence that cancer progression is associated with decreased NK cell cytotoxicity. However, not all studies show this relationship, and it must be borne in mind that the pathophysiology of exogenous implanted tumor is likely to be quite different from that of endogenous cancer. Furthermore, no causal inferences can be drawn from this evidence. The reduced NK cell activity might markedly impair immune surveillance and thereby foster tumor growth. On the other hand, the progression of disease might trigger a cytokine or other mediator that results in impaired NK cell function. However, the studies do suggest that stress, NK cell activity, and tumor progression may be related.

Neuroendocrine Effects of Stressors on Cancer Progression

The association between psychosocial stressors, endocrine shifts, and tumor proliferation has been well established in a number of animal studies. In a set of classic experiments, Riley (1981) showed that animals reared in crowded environments had much more rapid tumor progression than those raised in less stressful environments. The endocrine response to stressors involves a cascade of LHPA activity, in which levels of cortisol, the classic "stress hormone," are elevated. This stress response appears to be consistently elicited despite the nature of the stressor, with the same endocrine pattern being elicited from either physical or emotional stressors. Acute medical illness is associated with increased secretion of ACTH (Drucker and McLaughlin 1986), dehydroepiandrosterone (DHEA), and cortisol (Parker et al. 1985) and lowered DHEA:cortisol ratios (Ozasa et al. 1990), as is spousal bereavement (Irwin et al. 1987). The severity of the psychosocial stressor appears to be crucial, however. For example, elevated cortisol levels are seen during spousal bereavement (Irwin et al. 1987) but not under conditions of examination stress (Glaser et al. 1994).

The mechanisms by which stressor-induced hypercortisolemia stimulates tumor progression are only beginning to be understood. Several widely held theories predominate.

1. *Cortisol is immunosuppressive.* Glucocorticoids may stimulate tumor growth via an immunomodulatory effect. Chronic exposure to a stressor and elevation of glucocorticoids may result in immunosuppression and, therefore, tumor proliferation (Sapolsky and Donnelly 1985).
2. *Elevated cortisol levels may have some role in the stimulation of angiogenesis.* Another theory about the relationship between elevated cortisol and tumor growth includes the possible cortisol-related stimulation of angiogenesis, which leads to tumor vascularization and growth (Folkman et al. 1983).
3. *Glucocorticoids may have a differential effect on glucose metabolism in tumor cells, and this may lead to changes in energy utilization by*

normal cells. Cortisol and other glucocorticoids maintain high circulating levels of blood glucose during stressor exposure to stimulate gluconeogenesis and inhibit glucose transport into normal cells. However, tumor cells demonstrate greatly increased intracellular energy needs in order to sustain rapid growth and are believed to become resistant to glucocorticoid inhibition of intracellular transport, which leads to much of the substrate being shunted to the tumor (Romero et al. 1992). The tumor cells exhibit a shift in glucose metabolism from aerobic to anaerobic glycolysis, during which glucose is converted to lactate, which is then returned to host cells as a nonusable waste product (Dills 1993). Thus, a cycle is created under conditions of stress, in which elevated glucocorticoids selectively deprive healthy cells of glucose in order to maintain high circulating levels, with the result that the noninhibited tumor cells are greatly facilitated in obtaining the nutrition necessary to proliferate.

4. *Shifts in adrenal hormones other than cortisol may lead to increased tumor growth.* Some evidence indicates that the presence of other steroid hormones, especially the adrenal hormone DHEA, may directly oppose the action of cortisol and exert an inhibitory, rather than a stimulatory, effect on dysplastic transformation and malignant proliferation. In a study of rats inoculated with mammary tumor, rats who were adrenalectomized after initiation of tumor demonstrated greater tumor progression in the absence of glucocorticoids (Carter and Carter 1988). The addition of DHEA in the diet of rats with mammary tumor led to a significant decrease in both tumor promotion and progression (Ratko et al. 1991). However, in ovariectomized rats, the addition of DHEA enhanced, rather than slowed, tumor growth, and this suggests that the interaction with nonadrenal androgens may play a role in tumor growth as well (Boccuzzi et al. 1992).

Aging

Cancer is, by and large, an illness of middle to late life, being comparatively rare in young people. During the later stages of life, the

cortisol response to stressors becomes less flexible in its return to baseline and remains elevated for a longer period of time (Sapolsky et al. 1983). Cortisol elevation and related immunosuppression were found in depressed older, but not younger, adults (Schleifer et al. 1983). Sapolsky and Donnelly (1985) demonstrated that aged rats show increased tumor proliferation as well as slower recovery of corticosterone secretion after stressor exposure. They injected rats with Fischer fetal rat cells that had been transformed with Fujinami sarcoma virus. The young but stressed rats had a higher incidence of measurable tumors, and the older and stressed rats had substantial elevations in tumor weight. Thus, one possible explanation for the prevalence of cancers later in life is that the intrinsic immunomodulatory systems, particularly the adrenal corticosteroid system, are less well modulated and more easily disinhibited by stressors than they are earlier in life.

A significant body of evidence suggests that the endocrine-immune cascade ultimately moves toward an irreversible, downward spiral. Cancer cachexia, a hypermetabolic and hypercatabolic state of starvation, is typified by simultaneous, coexisting, contradictory states of weight loss and tumor growth. In a "normal" host, the "work" of starvation is characterized by a compensatory resting state manifested by 1) lowered energy requirements in the form of decreased basal metabolism and 2) a shift in substrate utilization from glucose to fat in an attempt to preserve muscle mass. In a cachectic cancer host, however, the requirement for energy and protein is increased, and protein (in the form of muscle mass), rather than ketones, becomes the preferred substrate for glucose production (Dills 1993).

Endocrinologic alterations in this state of deranged metabolism include a markedly activated LHPA axis, with increased secretion of "stress hormones" such as cortisol, ACTH, epinephrine, and glucagon. These changes progress and expand with increased physical stressors, a pattern implying that there is a "window of opportunity" in which lowering the burden of psychosocial stressors may translate into delayed tumor progression. In a study of neuroendocrine-immune parameters in 50 patients with advanced malignancy, Lechin and colleagues (1990) noted that patients with

continuous physical symptoms (such as pain and nausea) demonstrated increased baseline levels of plasma norepinephrine, epinephrine, and cortisol, as well as decreased platelet serotonin levels, when compared with similar subjects who were symptom-free. During periods of pain or nausea (symptom exacerbation), additional increases in plasma dopamine and free serotonin occurred, along with reductions in NK cell activity and lymphocyte number. Patients in terminal stages showed an overall lack of responsiveness of these mechanisms, with maximal decreases in all neurotransmitters and immunologic parameters.

Life Events as a Model for Stressors and Cancer Progression

The relationship between significant life stressors and subsequent immunosuppression has been clearly shown in events ranging from acute or chronic strain (e.g., academic examinations [Kiecolt-Glaser et al. 1986], caring for patients with Alzheimer's disease [Pagel et al. 1985]) to long-lasting sorrow and life change (e.g., bereavement [Bartrop et al. 1977] and divorce [Kiecolt-Glaser et al. 1987a]). Uncomplicated bereavement, for example, has been associated with increased mortality, change in lymphocyte cell numbers (altered CD4+ [T helper] and CD8+ [T suppressor] cell counts; decreased total lymphocyte counts), and altered function (impaired NK cell cytotoxicity; decreased lymphocyte mitogen response, despite steady state numbers of T and B cells) (Bartrop et al. 1977; Irwin et al. 1987; Schleifer et al. 1983). Even an external event as seemingly relatively trivial as taking an academic examination in medical school altered both cellular immune function (decreased lymphocyte proliferation to mitogen and reduced NK cell activity, increased plasma antibody titers to viral antigens, decreased cytokine production) and lymphocyte number (alterations in T cell subpopulations) (Dorian et al. 1982; Glaser et al. 1986; Kiecolt-Glaser et al. 1986).

The correlation between stressors and immunosuppression raises a twofold question: Can major life stressors 1) lead to the development of cancer in healthy persons or 2) accelerate disease pro-

gression in patients with preexisting cancer? Considerable controversy in the literature has occurred regarding the long-term physiologic sequelae of stressful life events in cancer patients. Some of the variability in results stems from the lack of methodologic uniformity and the relatively limited duration of follow-up in studies looking at this connection. A number of retrospective, case-control or matched studies have attempted to correlate greater severity of life events with the occurrence of malignancy (breast cancer and malignant melanoma) 5 or 6 years later (Forsen 1991; Geyer 1992; Havlik et al. 1992). However, circumstances of life stressors differ among the studies, and thus comparison of the results is difficult.

Conflicting results from two studies further illustrate the confusion surrounding the findings related to major life stressors and breast cancer progression. In the first study, Ramirez and colleagues (1989) studied a matched sample of relapsed versus nonrelapsed breast cancer patients and observed a higher prevalence of major life stressors in the recurrent group. These serious stressors included divorce, job loss, and forced relocation. The severity of stressor was crucial, with major stressors contributing only to an elevated risk of relapse. In contrast, in the second study, Barraclough and colleagues (1992) prospectively studied a group of breast cancer patients, 51% of whom experienced major life stressors during the 42 months of the study. Disease progression was evident in 23% of the total sample. The authors found no correlation between stressors and disease progression. One possible explanation for the conflicting results between these studies is the failure to correlate the level of distress during the stressor with the level of distress years later, by which time varying degrees of individual adaptation may have occurred.

Psychological and Immunologic Adaptation to Stressors

Exposure to chronic stressors does not necessarily result in immunosuppression. Although both acute and chronic stressors are

associated with adrenocortical dysregulation, the chronobiology (i.e., memory and state) of the immune system and the timing of the stressor appear to determine the direction of immunologic responsiveness. Both unexposed and previously exposed mice demonstrated decreased antibody production when foot-shocks were applied 72 hours following antigen administration. However, when the foot-shocks were applied immediately after inoculation, mice with prior exposure to the stressor (and therefore preexisting immunologic "memory") demonstrated immuno-enhancement sufficient to counteract the immunosuppression of stress (Zalcman et al. 1989).

Chronic exposure to stressors may also lead to immunologic adaptation (Sklar and Anisman 1979). One study involving more than 2,000 women presenting at a breast cancer screening clinic for routine checkup indicated that whereas experiencing a single, acute major life stressor may be associated with malignancy, regular exposure to stressors may actually reduce the risk of malignancy (Cooper and Faragher 1993). However, one could argue that those who survived such catastrophic events were naturally selected because their immune system was either more robust or less responsive to stressor-related changes.

The response to chronic stressors may differ from that to acute stressors in terms of both psychological symptoms and physiologic response. Some studies have noted partial immunoenhancement or even frank overactivation of the immune system in relation to chronic stressors. Dobbin and colleagues (1991) found that among subjects exposed to examination stressors, levels of interferon-γ and lymphocyte proliferation response to mitogen were decreased, whereas certain facets of immune function (IL-1 β level, monocyte blast transformation) were enhanced and intensified rather than suppressed. Internally perceived stressors such as job strain or poor social support have also been shown to lead to overactivation of the immune system (increased immunoglobulin production) rather than underactivation (Theorell et al. 1990). The endocrine system, which is reactive to stress, regulates aspects of the immune responses noted here. For example, autoimmune disease results

from certain endocrine deficiency states (Sternberg et al. 1992). Heterogeneity in the components of immune function measured, as well as in the nature and perceived meaning of the stressor, complicates the assessment of the interaction between stressors and immunity.

Having cancer can be considered a *chronic* stressor. Reminders of the illness are a daily occurrence, with arduous treatments providing additional sources of stressors. For some, cancer is also a *traumatic* stressor. The presence of traumatic distress symptoms, such as intrusive thinking, dissociation, and avoidant behavior, has been associated with the diagnosis of cancer (Alter et al. 1993), surviving cancer (Levy et al. 1991), and the diagnosis of recurrence (Cella et al. 1990). Although the distinction between types of psychological distress is seemingly minor, there is some evidence that type of psychological symptomatology is related to the degree of immune response to a stressor. A small study of medical students taking a national examination revealed that students who reported higher levels of psychological intrusion related to the event had significantly greater T cell decrements than did those who reported avoidance; however, both groups had changes that persisted for 4 weeks after the examination (Workman and La Via 1987). Holocaust survivors with cancer showed significantly greater psychological distress in the form of intrusion and avoidance than matched cancer patients but demonstrated the same level of functioning—a finding which suggests that active coping mechanisms may be intact in the survivors (Baider et al. 1992).

Thus far in this chapter we have seen that the endocrine-immune response to stressors may lead to significant immunosuppression and subsequent rapid tumor progression. This response is mediated by internal and external circumstances. The individual's interpretation of the severity of the stressor, personality and coping style, cognitive ability, prior exposure to stressors, and social support, as well as his or her baseline emotional well-being, all contribute to the degree of physiologic perturbations observed.

Internal Modulation of Tumor Progression

Mood

Depression and Cancer

Defining possible effects of depression on cancer has been a complex problem. Although it is well known that rates of depression are high among cancer patients (Derogatis et al. 1983; Spiegel et al. 1994), the hypothesis that depression may be associated with cancer incidence or progression has not been clearly established. Shekelle and colleagues (1981) initially showed that depression predicted higher cancer incidence. However, a later, large-scale study failed to confirm this finding (Fox 1989; Zonderman et al. 1989).

Approximately 20% to 50% of cancer patients have coexisting psychiatric diagnoses—most often, depression or anxiety disorder (Bukberg et al. 1984; Derogatis et al. 1983; Massie and Holland 1990). It is sometimes difficult to distinguish between a "normal" reaction to a diagnosis of cancer and one that manifests psychiatric illness. Before the advent of DSM-IV, which considers psychiatric symptoms in the presence of medical illness as a separate category, patients who were distraught over their cancer were frequently diagnosed as having an "adjustment disorder with depressed mood," or the symptoms of depression (e.g., hopelessness, low energy, and anorexia) were misattributed to the disease itself.

Much of the mood disturbance in cancer patients may, indeed, be related to factors surrounding diagnosis and treatment; however, a clear-cut temporal relationship appears to exist between certain malignancies and endogenous depression. For example, the link between pancreatic cancer and depression was first identified in 1923 (Scholtz and Pfeiffer 1923; see Green and Austin 1993). In a prospective study of patients presenting with possible intra-abdominal pathology to the Mayo Clinic, 76% of those found to have pancreatic cancer exhibited symptoms of major depression (Fras et al. 1967). Depression was the only prodromal symptom, either physical or psychological, in nearly 50% of these patients but

in only 17% of colon cancer patients. The varied presentations of depression among patients with malignancy, ranging from adverse psychosocial reactions to intrinsic biological components, suggest nonuniformity in the physiologic parameters as well.

Depression, Bereavement, and Immune-Endocrine Alterations

Depression has been clearly linked to diminished neurotransmitter (norepinephrine and serotonin) levels, decreased immunologic function, and endocrine aberrations. For example, a number of studies have demonstrated that baseline serum cortisol levels are elevated in patients with acute endogenous depression (Linkowski et al. 1987; Rubin et al. 1987, 1989; Sachar et al. 1973). This activation of neuroendocrine activity was associated with a corresponding decrease in NK cell activity in other studies (e.g., Sapolsky and Donnelly 1985).

Like depression, uncomplicated bereavement, undoubtedly a severe stressor, has been associated with elevated mortality, change in immune cell numbers (altered CD4+ and CD8+ cell counts, decreased total lymphocyte counts), and alterations in function (impaired NK cell cytotoxicity, decreased lymphocyte proliferation to mitogen despite steady state numbers of T and B cells) (Bartrop et al. 1977; Irwin et al. 1987; Schleifer et al. 1983). Bereavement and depression do not appear to be identical, however. It may be that physiologically the body reacts differently during depression than it does during bereavement. This is easily demonstrated in the studies examining immune-neuroendocrine changes in acute endogenous depression in vivo. Irwin and colleagues (1987) found that during bereavement there was an associated decrease in NK cell activity, but they did not find elevations in plasma cortisol levels.

Researchers have been unable to clearly establish a link between either depression and cancer or bereavement and cancer. As previously noted, although the literature suggests a connection between severe stressors and the presence of malignancy, this connection has failed to be established. A study of breast cancer patients, for

example, has shown that high life stressor level is associated with a greater likelihood of relapse (Ramirez et al. 1989). However, Barraclough and colleagues (1992), in a prospective trial, found no relationship between life stressors and cancer progression.

Some evidence indicates, however, that the flexibility of the neuroendocrine system may diminish with increasing age, leading to delayed recovery and a prolonged elevation of cortisol levels during stressful times (Sapolsky and Donnelly 1985). The immune response is also blunted during the later stages of life, and this leads to an increase in age-related immunosuppression (Goodwin et al. 1982). This increased immunologic vulnerability is translated into a greater prevalence of depression-related immunosuppression in the elderly in some, but not all, studies (Schleifer et al. 1983, 1984, 1989). This effect is strongest in older depressed patients, raising the possibility that it is due more to aging than to depression. Thus, one possible explanation for the prevalence of cancers later in life is that the intrinsic modulatory systems, particularly immunomodulatory systems, are less functional and more easily inhibited by stressors than they are early in life. This, in turn, may lead to increased tumor promotion.

Role of Antidepressants in Tumor Progression

The attempt to define the relationship between antidepressants and tumor progression has been confusing at best, with contradictory findings that have received considerable public scrutiny. Some of the confusion may result, in part, from methodologic inconsistencies, such as failure to induce animal models of depression before administering antidepressants versus paradoxical use of antidepressants to induce depression. These inconsistencies in tumor setting lead to difficulties in the interpretation of data regarding risk of tumor growth. For example, the administration of the antidepressant clomipramine in neonatal rats induces a state resembling human endogenous depression. In a study examining the effects of stressors on tumor growth, two groups of neonatal rats were inoculated with mammary tumor cells and then stressed through various handling techniques. Half of the animals were

treated with clomipramine to induce depression before tumor inoculation. A significantly higher proportion of the clomipramine-treated depressed rats, compared with the nontreated rats, developed mammary tumors and had shortened survival time. Interestingly, the nonhandled control rats fared even worse, having the greatest tumor growth and the shortest survival time overall (Hilakivi-Clarke et al. 1993). On the other hand, clomipramine has also been noted to augment chemotherapy effects. In an older, in vivo animal study, it was noted that the calmodulin-inhibiting activity of the antidepressant enhanced the effect of the chemotherapeutic agent vincristine in resistant leukemia cells (Tsuruo et al. 1983).

Early studies of the selective serotonin reuptake inhibitor fluoxetine found that it had no effect as either a complete carcinogen or a tumor promoter (Bendele et al. 1992). However, antidepressants commonly bind to intracellular histamine receptors that are associated with antiestrogen binding sites in microsomes and nuclei. Ligands associated with these sites have been found to stimulate tumor growth in vivo. Brandes and colleagues (1992) studied the in vivo effects of fluoxetine and amitriptyline on tumor growth administered at clinically relevant doses to rodents. From inoculation with either fibrosarcoma, mammary, or melanoma tumor cells, three separate indices of accelerated tumor growth were selectively applied. A significant correlation between antidepressant (both fluoxetine and amitriptyline) and stimulation of tumor growth was found for all three types of tumors.

The clinical significance of these findings is difficult to extrapolate. In the previous studies, administration of antidepressants to nondepressed animals led to the creation of a state of depression, which was followed by increased tumor elaboration. One possible interpretation of these discrepancies is that Brandes et al., by administering antidepressants to nonstressed (i.e., nondepressed) animals, created an animal state of depression, which subsequently led to accelerated malignancies. One such study of the effect of antidepressants on tumor growth in depressed animals was conducted by Basso and colleagues (1992). In a study of the effect of imipramine on tumor growth, a chronic variable stressor proce-

dure was used to induce an animal model of depression in rodents prior to their being inoculated with sarcoma cells. Half of the animals were pretreated with the potent immunosuppressant cyclosporine in order to facilitate tumor growth. In unstressed non–cyclosporine-treated rats, no tumor growth was evident. However, in all of the stressed animals, regardless of whether they had received cyclosporine, tumor growth was accelerated. The administration of imipramine after development of the tumor in stressed and/or immunosuppressed animals inhibited further tumor growth.

Some of the variation in the effects of antidepressants on tumor growth may be attributed to the differences between central and peripheral effects of neurotransmitters. In a study of stressors and immunosuppression in non–serotonin-depleted rats, administration of two substances that produce opposite effects on serotonin metabolism in the brain resulted in the same immunosuppressive peripheral effects. The first drug, 5-hydroxytryptophan, a serotonin precursor agonist, increases circulating levels of serotonin, whereas the second, parachlorophenylalanine, a serotonin synthesis inhibitor, decreases these serotonin levels. The neuroendocrine effects of the two agents were dissimilar, however, and this led to differing immunosuppression in the two groups. The rats administered parachlorophenylalanine demonstrated significantly elevated levels of plasma corticosterone in response to the stressor. This strong adrenal response may have obscured the weaker central serotonin antagonist effect on immunocompetent cells in that group (Boranic et al. 1987). In another study on the immunosuppressive effects of antidepressants, desipramine and maprotiline were found to have different effects (Eisen et al. 1989). Chronic treatment with maprotiline impaired NK cell function—both in vivo NK clearance of tumor cells from lung and in vitro NK cytolytic activity. Other measures of cell-mediated immunity, in the form of in vitro T and B lymphocyte proliferation and in vivo delayed hypersensitivity skin testing, were not affected by nontoxic doses of maprotiline. Desipramine, in contrast, showed no effect on NK activity in vivo or in vitro.

In summary, the evidence does not suggest that the clinical use

of antidepressants accelerates cancer progression. Effective treatment of depression, with its endocrine and immune correlates, should theoretically be helpful rather than harmful to cancer patients regarding the control of their disease. However, such a positive clinical effect of antidepressants on cancer progression has not yet been proven.

Cancer, Mental Illness, and Mood: Potential Immuno-enhancing Effects of Lithium and Neuroleptics

One confounding factor that arises in interpreting the associations among mood, medication, immunologic function, and tumor progression is the definition of the baseline in vivo host environment. A number of studies have attempted to determine whether the apparent lower-than-average cancer incidence among the mentally ill is related to the use of neuroleptic and mood-stabilizing medications. It is hoped that the investigation of patients who experience psychobiological extremes may eventually shed some light on the interrelatedness of these factors in the context of a less dramatic host environment.

The question of whether the incidence of cancer among individuals with chronic schizophrenia is reduced relative to that in the general population is unresolved. Certainly, many of the health behaviors of the chronically mentally ill are consistent with a higher rate of malignancy; yet, paradoxically, a number of studies suggest a lower incidence of cancer in this group. In a study of more than 9,000 schizophrenic patients in Denmark, Mortensen (1994) found a lower incidence of genital cancers (especially testicular) and skin cancers (including malignant melanoma), as well as a breast cancer risk equivalent to that in the general population. When these results were adjusted to take into account the smoking habits of the psychiatric patients, the risk reduction was significantly enhanced. However, in a similar study, Gulbinat and colleagues (1992) found no difference between populations. In a case-control study of prostate cancer risk among patients with schizophrenia, Mortensen and colleagues (Mortensen 1992) noted both a decreased risk of prostate cancer and a significant association with a higher cumulative

dose of high-dose phenothiazine (average daily dose of 145 mg of chlorpromazine for 12 years). Interestingly, in a second study by the same group, the risk of death from cancer in patients who had been diagnosed with reactive psychosis and not chronic schizophrenia was increased rather than decreased relative to the general population (Jorgensen and Mortensen 1992).

Current studies on immune function in schizophrenia are inconclusive. Stressor-induced immunosuppression may also play a role in the changes of cancer risk in schizophrenia independently of medication effects. In a study of NK cell activity in nonmedicated schizophrenic patients compared with matched control subjects, Wang (1987) found that baseline NK cell activity was higher in the schizophrenic group. The level of severity of symptomatology may play a role in the degree of immunosuppression. In a study of 33 hospitalized patients with first-episode schizophrenia, patients with more severe disease and negative symptomatology were noted to have lowered IL-2 production compared with those with less severe disease, among whom IL-2 levels were normal (Ganjuli et al. 1992). Moreover, early onset of psychotic symptoms correlated with greater immunologic abnormality.

An association between neuroleptic use and more aggressive forms of breast cancer—possibly resulting from chronically increased prolactin levels—has been suggested. Tsubura and colleagues (1992) reviewed the clinicopathological findings for 13 schizophrenic patients with breast cancer and noted a high incidence of both multiple tumors and lipid-secreting carcinoma cells. This association was not confirmed in the Denmark study (Mortensen 1994), however. In a double-blind, open-ended interview study of personality structure and breast cancer risk ($N = 77$), malignant breast tumors were diagnosed in 19 women categorized as having "poorly organized neurosis or psychosis," whereas no malignancies were detected among women described as having "well-organized neurosis" (Jasmin et al. 1990).

In vitro studies of chlorpromazine and other neuroleptics suggest that an antitumor effect exists. This effect is manifested in three ways: 1) interference with oxidative metabolism in tumor mitochondria (Jones 1985), 2) reversal of multiple drug resistance in

tumor cells (Akiyama et al. 1986), and 3) in vivo enhancement of chemotherapeutic response in resistant tumor (Hait et al. 1989; Miller et al. 1988). However, other studies have noted an in vitro immunodepressant effect of neuroleptics, in particular chlorpromazine (see Ferguson et al. 1975), as well as an in vivo immunodeficiency in medicated schizophrenic patients relative to immune measures in the general population (DeLisi et al. 1983; McDaniel 1990).

Lithium has also been noted to have both immuno-enhancing properties and an antitumor growth effect. Increased production of human T cells and IL-2 production (Haffman et al. 1981), as well as inhibition of T suppressor cell activity (Gelfand et al. 1979), has been reported. Wu and Yang (1991) found that IL-2 production in human and animal T cells was enhanced after in vitro treatment with lithium. In a subsequent study, Wu and Cai (1992) found that in vitro supplementation with lithium increased lymphokine-activated killer (LAK) cell activity in both human monocytes and mouse splenocytes. In addition, the level of tumor necrosis factor–α mRNA secreted by the LAK cells was increased, with the increase resulting in reduction of tumor size and prolongation of survival in tumor-bearing mice. Lithium may possibly have a direct effect on leukemic cells as well. Leukemia is a disorder of interrupted differentiation of hematopoietic cells. In vitro lithium induced terminal differentiation of these cells, a finding that suggests a possible role for this agent in leukemia therapy (Sokoloske et al. 1993).

Clearly, although there are no easy explanations for how the aforementioned factors influence immunity and tumor progression in the mentally ill, an apparent interrelatedness does exist. One potential explanation for the differences in cancer prevalence in this population may lie in the level of stress-induced activation of the neuroendocrine-immune cascade. It is possible that the nonresponsiveness of a blunted emotional response such as that observed in patients with chronic schizophrenia, or, conversely, pharmacological blunting of an overly activated response such as mania, may inhibit some of the immunosuppressive response to stressor that has been described in healthy populations.

Personality and Coping Styles

Is there a "cancer personality"? Subtle psychological factors such as coping styles, stressor responses, and personality variables have been noted to have an immunosuppressive effect (Lazarus and Folkman 1984; Temoshok and Dreher 1992). Attempts to associate these traits with cancer diagnosis and progression have met with only limited success, whereas studies associating these traits with immunosuppression have been abundant. Maladaptive coping styles, such as blaming, fantasy, or avoidance, were found to correlate with an immunosuppressive effect (Felton et al. 1984), as were passive stoicism, apathy, and self-blame (Levy et al. 1987; Pagel et al. 1985). Sieber and colleagues (1992) found that even the individual's perceptions and desires may have a negative effect. Among healthy volunteers, not only perceived lack of control over an unpleasant stimulus but also the simple desire to be in control was associated with a decline in NK cell activity. A similar study of coping among married men indicated that "non-copers" had not only decreased NK cell activity but also a decreased number of antigen-carrying markers on their NK cells (Schlesinger and Yodfat 1988). Surprisingly, positive personality variables such as optimism and an optimistic explanatory style, however, seem to negatively affect immune function, with subsequent decreased cutaneous responses to delayed hypersensitivity testing and diminished lymphoproliferative response to mitogenic challenge (Kamen et al. 1991; Sieber et al. 1992; Temoshok 1985).

In a prospective study of breast cancer progression in 52 women and 32 control subjects, cancer progression over a follow-up period averaging 624 days showed that neoplastic spread was associated with repression, reduced expression of negative affect, helplessness-hopelessness, chronic stressors, and comforting daydreaming (M. R. Jensen 1987). Interestingly, in an earlier study, Levy and colleagues (1985) found that lower NK cell activity not only was predictive of breast cancer spread to axillary lymph nodes but also was correlated with an observer's rating patients as "well adjusted to their cancer" such that women with higher NK cell activity were considered by observers to be distressed or "maladjusted." Al-

though spectators may prefer the patient to be pleasantly quiet, the immune system response does not justify this preference. Expression of intrapsychic distress appears to be a major component in relief of stressor effects and may contribute significantly to delay in tumor progression, as described later in this chapter (see also, e.g., Derogatis et al. 1979).

External Modulation of Cancer Progression

Cancer is in itself a stressor, with its threat of mortality, imposed social isolation, and the rigors of treatment (Spiegel 1990). In addition, it is not exclusively an individual disease. The diagnosis of cancer reverberates throughout the patient's social structure, including family and friends and the occupational, financial, spiritual, and educational arenas. These immeasurable effects often progress to become significant stressors in their own right, eventually contributing to stressor-related changes in immune and neuroendocrine function. In a study of an educational and coping intervention for women with breast cancer, immediate and longer-term decreases in levels of cortisol and increases in number of lymphocytes were observed in association with improvement in psychological distress (Schedlowski et al. 1994). Two aspects of psychosocial treatment interventions in cancer patients have consistently been found to influence cancer progression: social support and emotional expression.

Social Support

Of the five separately published studies examining the effects of psychosocial intervention in cancer patients, three have demonstrated that both the psychosocial and physical sequelae of malignant disease can be modulated by psychosocial interventions. Strikingly, in these three studies, in which improvement in both disease progression and overall survival was observed, the interventions had similar components. In these studies, patients were provided with social support, an arena for emotional expression,

and direction in coping with life-threatening illness.

Spiegel and colleagues (1989) randomly assigned 86 women with metastatic breast cancer receiving standard medical care to conditions of either treatment (weekly group therapy intervention) or control (nonintervention). The intervention technique used, supportive-expressive group psychotherapy, consisted of a weekly support group designed to encourage expression of strong emotion, address fears of death and dying, intensify mutual support, improve relationships and doctor-patient communication, and help patients manage pain through self-hypnosis. Women assigned to the intervention group lived an average of 18 months longer than those in the control group. By 48 months after the study began, all of the control patients had died, whereas one-third of the intervention subjects were still alive.

Richardson and colleagues (1988, 1990) randomly assigned lymphoma and leukemia patients to one of two groups: 1) a group receiving an active intervention consisting of home visits by a professional trained to deliver both education and empathic support, or 2) a control group receiving routine care. Not surprisingly, the intervention group demonstrated a significant improvement in adherence to medical treatment. However, independent of that effect, the intervention group had significantly longer survival times. This suggests that the educational benefits were extended by an enriching patient-caregiver relationship that also included support, coping, and empathy. Neither the duration of intervention nor the method of delivery (individual vs. group) appears to have negatively influenced the beneficial effect on both psychological outcome and prolonged survival.

Fawzy and colleagues (1990a) randomly assigned 80 malignant melanoma patients to either routine care or 6 weeks of an intensive group psychotherapy that included educational, expressive, and supportive components. At 6-month follow-up, the intervention patients had significantly better interferon-α–augmented NK cell activity (Fawzy et al. 1990b). This effect was not evident at 1-year follow-up. However, at 6-year follow-up, the intervention group had had significantly fewer recurrences and deaths (Fawzy et al. 1993). In this study, baseline NK cell activity predicted rates of re-

currence, and intervention status correlated with medical outcome. These findings raise the question of whether the timing of intervention (i.e., the time from diagnosis or treatment) may influence long-term outcome.

Two other studies showed no relationship between intervention and survival time. In both cases, the intervention was problematic. In the first, a matching study, participants with breast cancer in the Exceptional Cancer Patient Program were compared with breast cancer patients receiving routine care. No difference in subsequent survival time was observed (Gellert et al. 1993). In the second study, a randomized trial, breast cancer patients receiving a poorly defined assortment of group therapies that resulted in no psychological benefit also experienced no survival advantage (Ilnyckyj et al. 1994).

Overall, the findings on the effects of psychosocial intervention in cancer patients represent a small body of research, and further development is needed. However, three of five studies did indicate that the psychotherapeutic intervention had a significant positive effect on survival.

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Human beings are naturally communal animals, and lack of social community has been associated with an increased neuroendocrine-immune stressor response. Numerous studies in both animals and humans have shown that the presence of social support buffers this response, although not universally. To achieve a beneficial effect, the social support must be both adequate in quantity and nonconfrontational in quality. Support groups have been shown to 1) reduce feelings of isolation by providing a sense of universality among the members (Spiegel et al. 1981; Yalom and Vinogradov 1988), 2) decrease traumatic and psychological distress symptoms in both trauma victims and cancer patients (Marmar 1991; Spiegel et al. 1981), and 3) buffer the effects of stressful conditions (Kiecolt-Glaser and Greenberg 1984). In examining the differential response to added social support, three models can be identified: loneliness, communality, and stability.

Loneliness

Loneliness itself may be a sufficient stressor to impair immune response. For example, in one study of cynomolgus monkeys, those assigned to unstable social conditions with constant rearrangements of social groupings showed weaker lymphocyte proliferation responses to mitogen. This immunosuppressive effect was strongest among those monkeys who from the beginning demonstrated very little affiliative behavior (Cunnick et al. 1991). In studies of heterogeneous cancer patients, increased mood disturbance, decreased life expectancy, and decreased NK cell activity all correlated with a lack of social support (Ell et al. 1992; Jensen 1991; Levy et al. 1992; Waxler-Morrison et al. 1992). Reynolds and Kaplan (1990), in a reanalysis of the Alameda County Study data, showed that poor social support was related to higher cancer incidence in women and more rapid disease progression in men. Baile and colleagues (1992) investigated the relationship between depression and tumor invasiveness in a series of patients with cancer of the head and neck, a particularly disfiguring burden. Using a clinical interview and the Millon Clinical Multiaxial Inventory to measure dysthymia, they found two groups more likely to be depressed: 1) younger women with early-stage disease and 2) men with advanced cancer. These patients were also more likely to be unmarried.

Communality

The effect of social support as a buffer for stressful events has been elegantly demonstrated in a study of squirrel monkeys by Coe and colleagues (1988). When these animals were subjected to an aversive conditioned stimulus, the resultant stressor-related elevation of plasma cortisol was reduced when the animal had one of his companions with him during administration of the stressor. The cortisol increase disappeared entirely when the monkey was surrounded by five such companions. In this model, social support can be conceived of as a stressor buffer that may partially reverse the physiologic consequences of severe stressors.

Stability

A third, interrelated model of the effects of social support is that a secure social environment has beneficial effects on the brain by inhibiting or preventing development of a complete neuroendocrine-immune stressor response. Medical students who scored as "well supported" on the UCLA Loneliness Scale did not have stressor-induced immunosuppression at examination time, whereas those who reported themselves to be lonely did (Kennedy et al. 1988). Even the lower vertebrates demonstrate this effect. In a study of aggressive fish, social confrontation in the nonaggressors produced leukocyte immunosuppression (nonspecific cytotoxicity and mitogen-stimulated proliferative response). Some of this immunosuppression was reversed by administration of naltrexone, an opioid antagonist, a finding implicating at least partial mediation by endogenous opioids (Faisal et al. 1989).

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In addition, there may be a differential gender response to the effects of isolation and the addition of social support. In a prospective study of former medical students, those who developed cancer described a lack of closeness in parental relationships (Graves et al. 1991). Male cancer patients, however, described less satisfactory relationships overall. Two interesting differences were found in the gender-specific impact of stressful life events (McIntosh et al. 1993). The definitions of the stressors were different, as were the physiologic reactions to them. Men experienced lowered lymphocyte counts in response to internal distress, whereas women demonstrated elevated counts in response to both individual and family problems. The response to intervention appears equally beneficial in both genders, however (McIntosh et al. 1993).

Emotional Expression

The association between affect and neuroendocrine-immune shifts has been only preliminarily explored. In a study of laboratory

mood induction in healthy women, serum cortisol levels increased significantly during conditions of both sadness and elation, independent of arousal, but showed no change during neutral conditions (Brown et al. 1993). Interestingly, levels of human growth hormone rose during elation but did not change during the sadness or neutral states.

The act of disclosure as a component of expression also appears to be "good for your health." Subjects who disclosed personal trauma in journal form as part of a study design had both fewer doctor visits and improved immunologic function (Pennebaker et al. 1988). Although the meaning of these physiological perturbations is unclear, it is probable that normal expression of emotion is accompanied by neuroendocrine, and perhaps immune, alterations. If such alterations do occur, repression of strong emotion may be a stressor that directly leads to impaired immune and neuroendocrine function, either transiently or chronically.

Emotional expression in a supportive, empathic environment appears to be a key component in the reduction of psychological distress in cancer patients (Fawzy et al. 1990a, 1990b; Spiegel et al. 1989). Recent studies are beginning to explore the direct relationship between nonexpression of strong emotion and cancer progression. Several small studies have preliminarily found an association between suppression, nonexpression, and control of anger on the one hand and the presence of later-staged malignancies, as well as cancer progression and psychological distress, on the other (Swan et al. 1992). In a study of more than 2,000 women seen in a breast cancer screening clinic, the correlation between malignancy and a recent single acute life stressor was strongest for those women who were unable to express their emotions (Cooper and Faragher 1993).

As noted earlier, two published studies of psychosocial intervention in the treatment of cancer patients demonstrated no survival benefit in the intervention groups (Gellert et al. 1993; Ilnyckyj et al. 1994). The first study, by Gellert and colleagues (1993), was a follow-up on the Exceptional Cancer Patient Program developed by Dr. Bernie Siegel (1986). Gellert et al. found no difference in mortality between intervention patients and matched control subjects at 10-year follow-up. The intervention, which centers around

the use of "positive" thoughts, places much of the "work" of fighting cancer in the patient's own internal psyche. Results from the second study suggest that the skill and training of the therapists in eliciting expression may also play an indirect role in outcome. Ilnyckyj and colleagues (1994) reported no survival advantage for breast cancer patients who had received a poorly defined psychological intervention led by untrained therapists. The lack of survival advantage in this study is not surprising, however, in light of the absence of significant psychological benefits. These two negative survival outcome studies may have been limited by the nature of the psychological intervention.

In the three previously cited studies (Fawzy et al. 1990a, 1990b, 1993; Richardson et al. 1988, 1990; Spiegel et al. 1989), the expressive components of the interventions consisted of open patient expression of "negative thoughts" (e.g., fear of dying, anger, hopelessness) and correlated with improved psychological and physiologic outcome. Studies of expression of "positive thoughts" have not demonstrated a similar effect. In both cancer and noncancer patients, "positive" personality variables such as optimism and an optimistic explanatory style seem to negatively affect immune function, leading to decreased cutaneous responses to delayed hypersensitivity testing and diminished lymphoproliferative response to mitogenic challenge (Kamen et al. 1991; Sieber et al. 1992; Temoshok 1985).

Effects of Humor on the Neuroendocrine-Immune Axis

Ever since Norman Cousins (1976) first wrote about his own experience with the healing power of laughter, the role of humor in delaying disease progression has been suggested (Fry 1992). Humor has been linked to reduced distress, improved coping, and decreased depressive symptoms, as well as higher generativity (Carver et al. 1993; Halley 1991; Hampes 1993; Nezu et al. 1988). In a study of 59 breast cancer patients reporting their level of overall optimism during the first postoperative year, acceptance and the

use of humor were predictive of lower distress levels (Carver et al. 1993).

Several small but interesting studies have examined the neuroendocrine-immune effects of humor in healthy subjects. Berk and colleagues (1989) examined the endocrine changes that occur during "a mirthful laughter experience." Subjects watching a humorous videotape demonstrated reduced levels of cortisol, dopamine metabolites, epinephrine, and growth hormone compared with those who had not seen the tape. Similarly, humor has been found to be immuno-enhancing. Students exposed to humor demonstrated significantly increased salivary immunoglobulin A (IgA) compared with their IgA levels after exposure to didactics (Dillon et al. 1985). The use of humor as relief from the stress of daily "hassles" also has been shown to lead to a decrement in salivary IgA levels (Martin and Dobbin 1988). The laboratory measurement of salivary IgA has been plagued by methodologic inconsistencies, however, and this makes it a suboptimal measure of emotional distress (Kugler 1991).

The duration of the physiologic benefits from humor is unknown. A childhood history of humor (as an explanatory and coping style) was not found to correlate with increased longevity in later life; this suggests that the physiologic benefits may be transient rather than permanent (Friedman et al. 1993). Although it is clear that the physiologic effects of mirth are momentarily favorable, it has yet to be determined whether humor has an enduring effect on disease progression.

Conclusion

The available literature on psychoneuroimmune-endocrine effects on cancer is tantalizingly suggestive but not definitive. There is clear evidence that psychological and social stressors may evoke subtle, powerful perturbations within the neuroendocrine-immune cascade. Since this internal ecosystem is partly responsible for the way in which the body modulates disease progression, stressor-induced disturbances are likely to influence both the rate

of cancer progression and overall survival. The individual psychosocial and physiologic variables that predict responsiveness to intervention have not yet been determined, although the literature suggests that there is a lack of immune-endocrine responsiveness in very advanced disease.

It is now apparent that social support and emotional expression can, in certain instances, buffer stressor-induced immune and endocrine alterations and potentially lead to prolonged survival. The three studies that demonstrated improved survival were similar in content, with an emphasis on support, expression, and coping, but very different in structure and organization, ranging from time-limited, intensive group psychotherapy (Fawzy et al. 1990a) to home visits (Richardson et al. 1989) to ongoing weekly group therapy (Spiegel et al. 1989).

Interestingly, the content and the timing of intervention appear to independently influence disease progression. Few studies have examined the effects of intervention in terms of timing (earlier vs. later in the course of the disease). It is reasonable to suggest that histologic virulence and quantity of tumor burden may be rate-limiting factors. In Spiegel et al.'s (1989) study involving metastatic breast cancer patients, early mortality in the intervention group correlated with more advanced cancer, a finding which suggests that there is a powerful physiologic downward spiral that does not respond to external manipulations. Possibly, immune function is less impaired earlier in the course of the disease, when the burden of defense is smaller, allowing an early window in which psychosocial stressors have a substantially more significant impact on immune function. The implication then would be that psychosocial intervention may affect what is essentially an autonomous drain on immune function occurring in the presence of malignancy but not because of it.

As we have seen, the results from studies related to psychosocial factors, stressors, and disease progression are conflicting but suggestive. When survival outcomes differ, obvious methodologic differences can be found. Studies yield conflicting results in areas such as the relationship between stressors and relapse in breast cancer. Some, but not all, studies of psychosocial intervention

show a delay in disease progression. Nonetheless, there is sufficient evidence of stressor- and support-induced modulation of the immune system and of the clinical salience of these effects in modulating the rate of disease progression. Further investigation is clearly warranted.

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Chapter 6

Longitudinal Psychoneuroimmunologic Relationships in the Natural History of HIV-1 Infection: The Stressor-Support-Coping Model

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The asymptomatic stage between primary infection with human immunodeficiency virus type 1 (HIV-1) and progression to early symptomatic status and eventually AIDS is associated with various but increasing degrees of immunocompromise. The interval from HIV-1 infection to progression to AIDS is highly variable, as is the clinical course of AIDS after diagnosis and survival

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time. The rate of decline for immune system measures is neither consistent over clinical disease progression nor constant across individuals (Detels et al. 1988), and the decline may continue in the absence of clinical symptoms. It has been estimated that only 2% of those infected with HIV-1 develop AIDS within 2 years and that only 11% develop AIDS within 4 years. Average estimates of the time period from initial infection to progression to AIDS range from 8 to 10 years, and this period is lengthening as new treatments are developed. Behavioral factors may contribute significantly to the substantial individual variability in the interval from HIV-1 infection to AIDS (Goodkin 1990a). Specifically, an individual's psychosocial functioning may have important influences not only on his or her mental health but also on immunologic measures and physical health.

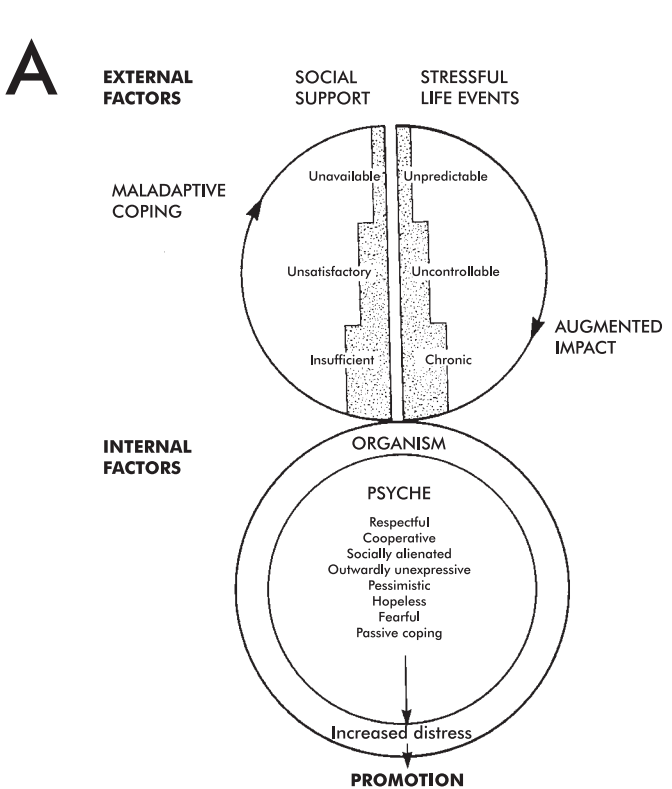
Recent research examining the effects of psychosocial factors on HIV-1 infection has yielded contradictory results. Whereas some studies have demonstrated such effects (Burack et al. 1993; Evans et al. 1995; Goodkin et al. 1992a, 1992b, 1994a, 1994b, 1995, 1996, 1998; Ironson et al. 1990; Kemeny et al. 1994), others have not (Kessler et al. 1991; Lyketsos et al. 1993; Perry et al. 1992; Rabkin et al. 1991; Sahs et al. 1994). This disagreement may derive from differences in methodology (Goodkin et al. 1994a, 1996; Kiecolt-Glaser and Glaser 1988). Specifically, the strategy of representing the entire psychosocial domain as a single variable—frequently a measure of distress, anxiety, or depression—and then correlating this variable with multiple immune outcome measures is inadequate in testing a potential role of behavioral factors in the progression of HIV-1 infection. Furthermore, for each immune outcome measure there frequently are many control variables in addition to the psychosocial variables themselves that need to be considered. In the case of immune outcome measures, use of prescribed medications (antiretroviral agents such as zidovudine, didanosine, zalcitabine, stavudine, lamivudine, saquinavir, ritonavir, indinavir, nelfinavir, nevirapine, delavirdine; and immunostimulants), lifestyle factors (e.g., cigarette smoking, caffeine intake, alcohol consumption, recreational substance use, sleep deprivation, exercise, and sexual activity), and nutritional status (in-

cluding specific micronutrients) represent controls of interest. Several of the foregoing (e.g., alcohol use, exercise, and recreational substance use) may also have to be considered as controls in predictions of psychological distress. For examination of physical health, in addition to the foregoing control factors, access to health care and the use of prophylactic medications for lethal complications of HIV-1 infection (e.g., rifabutin for *Mycobacterium avium-intracellulare* infection) are important.

The Stressor-Support-Coping (SSC) model proposed by Goodkin and colleagues (Goodkin 1987, 1989; Goodkin et al. 1990b, 1993a, 1993b, 1994, 1996, 1998, 1999) for the analysis of the progression of cervical high-risk human papillomavirus (HPV) infection to cervical intraepithelial neoplasia (CIN) is noteworthy in the context of progression of asymptomatic HIV-1 infection to AIDS as well (Figure 6–1). This model more fully characterizes an individual's context of psychosocial functioning and can be applied to the psychological, immunologic, and physical well-being of the HIV-1-seropositive individual.

In the SSC model, the psychosocial domain is conceptualized as comprising two spheres: the external and the internal. To the extent that life stressors within the external sphere are unpredictable, uncontrollable, and chronic, they are more likely to cause disruptions to an individual's psychological well-being (and thus increase psychological distress), immune function, and physical health. To the extent that these factors have been studied, uncontrollability seems to take precedence over unpredictability in determining deleterious physical health outcomes (Goodkin et al. 1993b). The impact of life stressors may be mediated by another component of the external sphere, social support; social support that is insufficient, unsatisfactory, and unavailable, respectively, can have progressively limiting effects.

Moreover, social support affects immune measures and physical health in the absence of any interaction with stressful life event count or impact. The factors in the internal sphere involve an individual's coping processes and attitudes. To the extent that an individual is overly respectful and cooperative, socially alienated, unexpressive of emotions, pessimistic, hopeless, fearful about so-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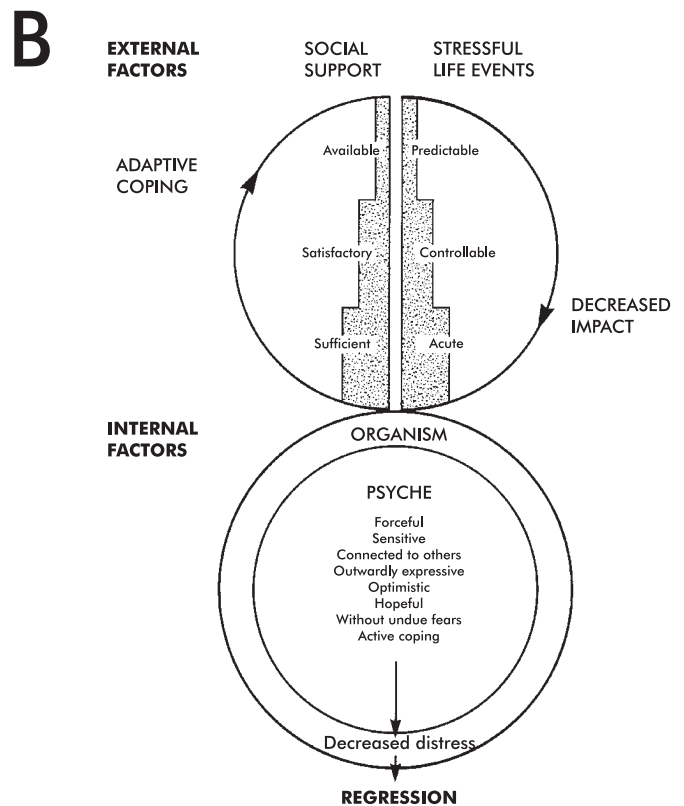
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INTERNAL FACTORS
ORGANISM
PSYCHE
Forceful
Sensitive
Connected to others
Outwardly expressive
Optimistic
Hopeful
Without undue fears
Active coping
Decreased distress
REGRESSION

Figure 6–1. The Stressor-Support-Coping (SSC) model for the role of psychosocial context in the progression of human papillomavirus–associated cervical intraepithelial neoplasia, HIV infection, and other immuno-modulated diseases. **(A)** In the *external* sphere, unpredictable, uncontrollable, and/or chronic stressful life events and unavailable, unsatisfactory, and/or insufficient social support can lead to increased impact on the individual and to psychological distress. In the *internal* sphere, to the extent that a person is overly respectful and cooperative, socially alienated, and outwardly unexpressive, pessimistic, hopeless, and fearful and reliant on passive coping styles, increased or higher levels of psychological distress will be more likely to ensue. Higher levels of psychological distress and increases over time are postulated to be associated with promotion of clinical disease progression. **(B)** Within the *external* sphere, when stressful life events are predictable, controllable, and acute, and social support is available, satisfactory, and sufficient, there is a decreased tendency toward psychological distress. In the *internal* sphere, the more forceful, sensitive, connected, outwardly expressive, optimistic, hopeful, and without undue fears an individual is, and the more likely the individual is to actively cope with problems, then the more likely it is that there will be decreased or lower levels of psychological distress. Lower levels of psychological distress and decreases over time are postulated to be associated with a greater likelihood of stabilization or regression of clinical disease.
Source. Reprinted from Goodkin K, Antoni MH, Sevin B, et al.: "A Partially Testable Model of Psychosocial Factors in the Etiology of Cervical Cancer, II: Psychoneuroimmunological Aspects, Critique and Prospective Integration." *Psychooncology* 2:99–121, 1993. Copyright 1993, John Wiley and Sons, Ltd. Used with permission.

matic status, and reliant on a passive coping style, the deleterious impact of life stressors is potentially enhanced in three outcome spheres: psychological well-being, immune function, and physical health. Conversely, availability of sufficient and satisfactory social support, utilization of active coping strategies (e.g., taking constructive action, planning a strategy), and positive attitudes (optimism, hopefulness, lack of undue somatic preoccupation, social connectedness, adequate emotional expression) will lessen the potential deleterious impact of external factors and may have direct, salutary effects in the three outcome domains.

Coping has two main attributes: dispositional style and situation-specific coping strategy. Response to stressful life events based on internal resources may be limited by maladaptive coping, especially when the individual has a coping repertoire composed of denial, distraction, and avoidance. This form of dispositional coping is more likely to have a maladaptive impact in the first of the three linked outcome spheres—psychological well-being. Because of associated neuroendocrine activation of the sympathetic adrenomedullary system and the limbic-hypothalamic-pituitary-adrenal axis, decrements in the second domain, cellular immune measures, including lymphocyte proliferation to mitogen, natural killer (NK) cell cytotoxicity, and human immunodeficiency virus (HIV)–specific cytotoxic T lymphocyte function, may be observed. Associated increments in the viral load of HIV-1 would be predicted to relate to changes in the third domain, physical health, with more rapid clinical disease progression and decreased survival time.

It can be concluded that factors in the internal (coping and attitude) and external (life stressors and social support) spheres can affect, directly or indirectly, the three outcome domains (psychological well-being, cellular immune measures, and physical health). The outcome domains themselves are interrelated. Research, as reviewed by Kiecolt-Glaser et al. (1992) and Maier et al. (1994), has demonstrated that psychological distress affects immune function and that immune function, in turn, affects disease progression and physical health. There is also the potential for feedback effects in the opposite direction—from the immune

system to behavior (e.g., via CNS effects of peripherally secreted cytokines).

On the basis of the SSC model of cervical cancer, Goodkin and colleagues (1994a, 1995) proposed that an understanding of the role of psychosocial factors in HIV-1 infection could be organized around the SSC model: the effect of life stressors, social support, and coping style predictor domains on the psychological, immunologic, and physical health outcome domains. Part of this theoretical perspective is the notion that life stressors—especially uncontrollable, unpredictable, severe and chronic ones—are associated with phenotypic (e.g., CD4 cell counts) and functional (e.g., decreased cytotoxic T lymphocyte killing) immune changes associated with disease progression. Goodkin et al. (1994a, 1995) specifically hypothesized that passive, maladaptive coping style, and attitudes of pessimism, hopelessness, and somatic anxiety as well as unavailable, unsatisfactory, or insufficient social support, increase the deleterious impact of life stressors and lead to increased psychological distress, which, in turn, is related to decreased cellular immune function and more rapid disease progression.

In this chapter, we detail some methodologic points that we feel are important to incorporate into investigations of the effect of psychosocial functioning on psychological well-being, immune status, and physical health. We then present findings from a study on the natural history of HIV-1 infection conducted at the University of Miami School of Medicine. Results in all three outcome domains—psychological well-being, immune function, and physical health—are presented, with the methodologic considerations taken into account.

Methodologic Considerations

When models with multiple determinants, such as the SSC model, are being implemented, it is fundamental to use a multivariable methodology such as multiple regression. It may be impossible to get a contextual viewpoint of the effect of life stressors, for example, without also including the effects of social support and coping

strategies. Consider the case of an individual with a high burden of negative life event stressors who also has an extensive social support network and actively copes with problems. This person will probably exhibit much less psychological distress than an individual with the identical level of stressors but minimal social support and a tendency to cope passively. In any particular sample, even when a strong relationship exists, it will not be evident in a simple correlation of stressors with distress because such a correlation does not control for the patterns of social support and coping in the sample. This problem has been referred to as *regression suppresor/inducer condition* (Pedhazur 1982) or *omitted variable bias* (Maddala 1988).

Just as it is important to control for the effects of other aspects of the domain when testing the variables of the psychosocial domain, it is essential to include in the analytical framework variables outside of the domain being tested that have strong relationships with the dependent variable. The list of variables for potential inclusion may be quite large, and this may necessitate using a method to reduce the number of variables so that only the most important are included in the analysis. First, only variables that have strong a priori justification for a relationship with the dependent measure should be considered. However, the number of potential control covariates remaining after such a selection process may still exceed the limits of the particular sample size.

We have successfully used a two-stage method to significantly reduce the number of variables. In the first stage, zero-order correlations are estimated between every potential covariate that is theoretically judged to be important and the dependent measure of interest. Then, only those variables for which the P value is less than 0.20—a conservative level—are included in the second phase. The 0.20 level of probability, while somewhat arbitrary, is chosen to ensure that important variables are included. Type I error is not the concern in this case; rather, the concern is that we capture and control for variables that should be included in the multiple regression model for testing the hypotheses. In the second stage of this control selection procedure, all control variables meeting the 0.20 probability criterion on the zero-order correlation with outcome

are entered into a multiple regression predicting this measure. Only variables that also have a β coefficient with a *P* value of less than 0.20 from this multiple regression stage are retained in the final hypothesis tests of the model.

This method ensures that those potential control covariates that are most directly related to our hypothetical model will be included. Inclusion of these variables will reduce residual variance in the final model test, which will improve the precision of the final estimates. However, this method cannot guarantee that all important control variables will be included. As within the model itself, it is important to include all control variables within the sphere of the specific outcome tested (deletion of any such variable might cause others variables inappropriately to appear unimportant because of omitted variable bias). In some conditions, certain control variables may show a strong relationship only when the model variables of interest are included in the regression. The only way to uncover these cases (in the absence of very large sample sizes) is to perform multiple tests of the model variables with various subsets of control variables. We find this approach unacceptable, however, because of the effect of multiple tests on the true α rate of the model test. Another potential procedure for the reduction of control variables—principal components or factor analysis—also could be employed. However, we have not used this method since many of the control variables that need to be considered are disparate in nature and any composite variable would be difficult to interpret or replicate in other samples.

The distribution of particular variables may also present a problem for estimation. Before any data analyses are conducted, the frequency distributions of each variable of interest should be examined for deviation from normality (or whatever distribution is required by the estimation procedure to be used). Frequently, a transformation may be employed to bring the variable closer to a normal distribution. We have routinely used log 10 transformations for mitogen response data, for example. There may be more subtle distributional problems for which a transformation may not be available, such as the presence of outliers in the data. Dropping of outliers that cannot be determined to have resulted from docu-

mented errors (e.g., in a laboratory assay) should be avoided, because valuable information may be lost (MacDonald and Robinson 1985). For simple correlations, a Spearman rank correlation (correlation on ranked values) will correct for the distortion due to inclusion of outliers without the loss of information that would result from dropping the outliers. In the case of multiple regression analysis, a useful solution is to rank all variables and perform the multiple regression analysis on ranked values (Conover and Iman 1981, 1982). This procedure is a helpful routine check for all parametric multiple regression analysis results to ensure they are not driven by distributional anomalies. There is also the potential for relationships to be hidden by such distributional problems. Divergence of results between the standard multiple regression procedure and regression on ranked values is an indication of distributional problems that were not noted in data preparation and quality control procedures.

We have emphasized that it is important to consider a complete, contextual categorization of the psychosocial domain to uncover a true picture of its effects on the three outcome domains of interest (psychological distress, immune function, and physical health). We can take this argument one step further and specify that these three predictor and three outcome domains need to be considered jointly in one single, coherent model. This can be accomplished with a path analytic (structural equations) model in which the interrelationships of the three dependent measure domains are examined and the role of the independent variable domains—life stressors, social support, and coping style—is tested across all three outcome domains. Structural relations models allow one to test the feedback effects of each domain—for example, effects such as notification of one's CD4 cell count or the appearance of HIV-1-related symptoms would be tested for a subsequent association with psychological distress, which in turn might affect subsequent immune status and physical health. Although a detailed discussion of this complicated approach is beyond the scope of this chapter, the research summarized here is a necessary first step in constructing a system linking the three outcome domains.

Analyses from the Natural History Cohort

A cohort of 118 HIV-1-seropositive and 54 HIV-1-seronegative homosexual men (control group) was followed at 6-month intervals for up to 42 months (depending on when subjects enrolled during the course of this 5-year study). All of the individuals in this cohort were volunteers who knew their serostatus. At entry into the study, HIV-1 antibody–seropositive individuals had persistent generalized lymphadenopathy, early symptoms of HIV-1 infection (e.g., constitutional symptoms, oral thrush, oral hairy leukoplakia), or a CD4 cell count of less than 700 cells/mm^3. Subjects were recruited from the University of Miami School of Medicine Clinical Research Unit, from community-based HIV-related service agencies, through referrals from community physicians, through advertisements in magazines with a gay male readership, and from referrals from study participants. The criteria for inclusion in the study were 1) not taking antiretroviral medication (e.g., zidovudine) or immunomodulators or participating in an HIV-1-related drug trial at study entry; 2) no history of excessive alcohol or substance use; 3) no history of severe head trauma or evidence of CNS disease or major psychiatric disorder; 4) ability to read and understand the assessment battery; and 5) willingness to be followed for the duration of the study. The subjects had scheduled appointments at 6-month intervals for venipuncture, after which selected immune parameters were quantified, extensive psychosocial and neurocognitive assessments were administered, and a physical examination was completed.

Psychological Distress

The psychological measures for the HIV-1-seropositive participants in our study—homosexual men with disease at a relatively early stage—were found to be closer to the norms of nonpatient populations than to any reported patient population norms. However, a subset of distressed individuals were identified as having clinically elevated scores on the Anxiety, Dysthymia, or Major Depression scales of the Millon Clinical Multiaxial Inventory II

(Millon 1987). Likewise, the coping styles and perceived social support of the sample as a whole appeared to be close to survey norms and to those of the HIV-1 antibody–seronegative control group. HIV-1-seropositive subjects reported significantly higher numbers of negative life event stressors and higher levels of psychological distress, as measured by the Profile of Mood States (POMS; McNair et al. 1971), than did HIV-1-seronegative control subjects (Blaney et al. 1990).

When the SSC model relationships of negative life stressors, social support, and hardiness in terms of psychological distress were examined in an investigation of baseline measures, life stressors showed a strong positive relationship, and social support showed a negative relationship, with observed levels of psychological distress (Blaney et al. 1991b). This early investigation did not include measures of coping style, per se, though hardiness was conceived of in terms of dispositional coping attributes.

Subsequent baseline analyses of the SSC model were conducted with a larger sample ($N = 134$). These analyses excluded hardiness and included four specific measures of dispositional coping—active coping, disengagement and denial, focus on and venting of emotions, and turning to religion. There was a trend for passive coping styles (as measured by disengagement and denial and focus on and venting of emotions) to be associated with higher levels of distress. In these analyses, negative life stressor count was positively related to psychological distress for both HIV-1-seropositive ($\beta = 1.85$, $P < 0.0001$, $n = 89$) and HIV-1-seronegative ($\beta = 2.68$, $P < 0.0008$, $n = 45$) individuals (Figure 6–2), with the size of the β weight indicating that this relationship was slightly more pronounced in the HIV-1-seronegative individuals. Social support was found to be inversely related to psychological distress only for the HIV-1-seropositive subsample ($\beta = -0.64$, $P < 0.02$). The HIV-1-seropositive individuals had higher distress than the HIV-1-seronegative individuals when all psychosocial and control variables were controlled ($P = 0.04$). Control variables that were significant ($P < 0.20$) for these cross-sectional analyses included caffeine intake and current psychoactive substance use.

In a longitudinal investigation of the SSC model in HIV-1-

seropositive individuals who remained asymptomatic for 12 months (i.e., three assessments), the relationship between changes in negative life stressors, perceived social support, and coping styles and changes in psychological distress again showed the importance of considering these domains jointly when investigating psychosocial outcomes (Blaney et al. 1991a, 1997) (see below). In this investigation, both direct (main) effects and stressor buffering (interaction) effects were observed when these predictors were jointly controlled in a multiple regression analysis.

Although our focus in this longitudinal study was to examine changes in the three SSC model predictor domains (life stressors, social support, and coping style) and their associations with changes in psychological distress, we also examined how these changes interacted with the absolute levels of these predictor do-

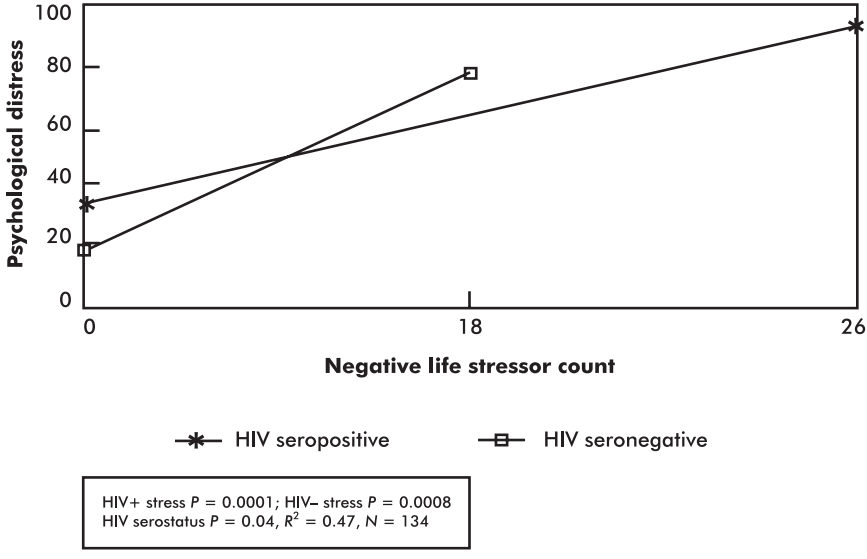

Figure 6–2. Relationship between negative life stressor count and psychological distress in a sample of men from the Natural History Cohort grouped by HIV-1 serostatus. Life stressors were found to be positively associated with the level of psychological distress in both groups. The range of life stressors was larger in the HIV-1-seropositive group.

mains. We found that changes in distress were inversely related to changes in perceived social support and turning to religion but directly related to changes in negative life stressor burden and to coping style (both disengagement and denial and focus on and venting of emotions). In addition, when examining interactions of these effects (involving changes) with the absolute level of the same predictors, we found evidence of nonlinear relationships for both life stressors (Figure 6–3A) and social support (Figure 6–3B). Specifically, variation in negative life event stressor count had greater impact on distress at lower levels of negative life events than at higher levels of such events. Likewise, variations in social support had greater impact on distress at lower levels of social support than at higher levels of such support. In other words, incremental social support reduces distress more, and incremental negative life events increase distress more, when levels of the respective predictors are low (Figures 6–3A and B).

When looking at potential stressor-moderating effects of the social support and coping style domains on predictions of psychological distress, we found moderating effects for social support and active coping style. These effects were robust to inclusion of the control for the nonlinear relationships discussed earlier. Specifically, social support showed an expected stressor-moderating effect (increases in social support had their greatest stressor-attenuating effect as life stressor impact was at greater increments) (Figure 6–3C). The effect for active coping style was diametrically opposed. Active coping style did attenuate the distress-inducing effects of negative life event stressors, but this effect was greatest at smaller increases in life stressor impact and diminished as stressor impact rose (Figure 6–3D).

In a subsequent analysis, again focusing on change scores, we compared subjects in the asymptomatic and symptomatic stages of infection. We found that changes in the level of life stressors were of less importance in increasing distress and that changes in social support were of greater importance in decreasing distress for the symptomatic subjects (Figures 6–4A and 6–4B). These findings are consistent with the increasing levels of stressors that occur with the experience of symptoms, since the analysis with asymptomatic

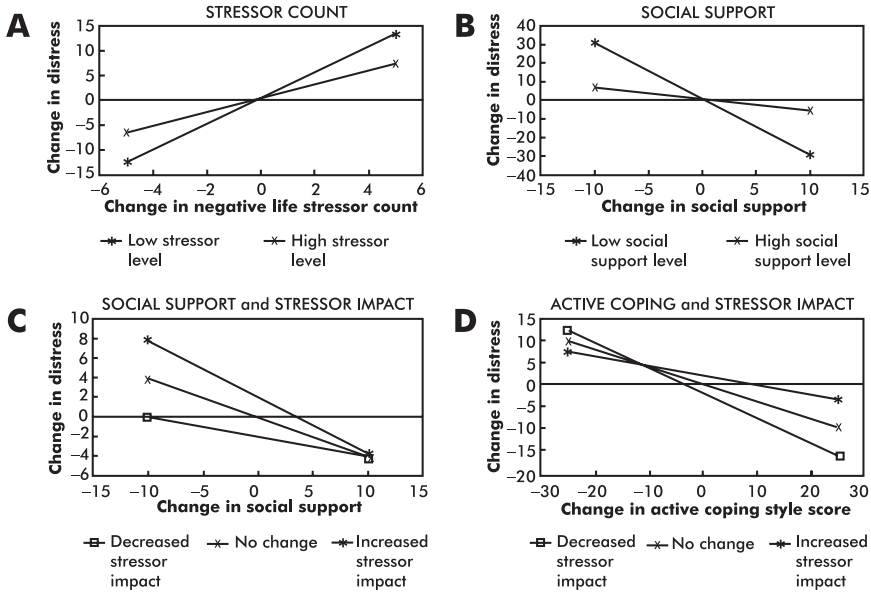

Figure 6–3. Relationship between changes in SSC model predictor domains and change in psychological distress, and their interaction with absolute levels of these measures, in a longitudinal investigation of the SSC model with a sample of HIV-1-seropositive individuals from the Natural History Cohort who remained asymptomatic for 12 months ($N = 40$; $N_{\text{time periods}} = 120$). **(A)** *Effect of change in stressors on change in distress.* Increased life stressor burden was associated with increased levels of psychological distress, but this increment diminished at higher life stressor levels. **(B)** *Effect of initial level and change in social support on change in distress.* Increased social support was associated with decreased psychological distress, but this decrement diminished at higher levels of social support. **(C)** *Effect of change in social support by change in stressor impact on change in distress.* The decrease in psychological distress associated with an increase in social support was largest when life stressor impact was increased. **(D)** *Effect of change in active coping by change in stressor impact on change in distress.* Increased active coping was associated with decreased psychological distress, but this effect was reduced as life stressor impact increased.

subjects indicated that the effect of negative stressors was nonlinear, with increments at the higher end of the range having less effect (Figure 6–3A). These findings, along with the earlier finding that, as the interaction of stressor levels with social support showed (Figure 6–3C), incremental social support is most effective at reducing distress as stressor impacts increase, may explain the increasing importance of social support as HIV-1 disease progresses.

Immune Function

Our investigation of the SSC model's relation to immune measures in the Natural History Cohort initially focused on NK cell cytotoxicity, a measure of cellular immune function that, compared with the CD4 cell count, is not as directly affected by HIV-1 infection (Goodkin et al. 1992a). In this study, we examined how negative life stressors, social support, and coping styles affect NK cell cytotoxicity in a cross-sectional model, controlling for prescribed medication use, lifestyle, and nutritional status variables. The study sample for this analysis comprised 62 asymptomatic HIV-1-seropositive individuals.

Potential control variables were examined by Spearman rank correlations for an association with NK cell cytotoxicity. Categorical variables were used for levels of current and past alcohol use, cigarette smoking, and recreational substance use (opioids, cocaine, amphetamines, nitrites, LSD, and marijuana). Current caffeine intake and use of prescribed medications were also included. Nutritional control variables included plasma levels of retinol binding protein, prealbumin, and serum albumin as indicators of acute, subacute, and chronic macronutrient status, respectively. Other nutritional variables included retinol (a dietary source of vitamin A), pyridoxine (a form of vitamin B_6), cobalamin (vitamin B_{12}), and zinc intake and plasma levels. A red blood cell zinc level was also obtained to examine long-term effects of this micronutrient. Intake of omega-3 polyunsaturated fatty acids and selenium was also examined. The foregoing control variables were selected because prior research had indicated their potential effects on cellular immune measures (Baum et al. 1991, 1995; Beisel et al. 1981;

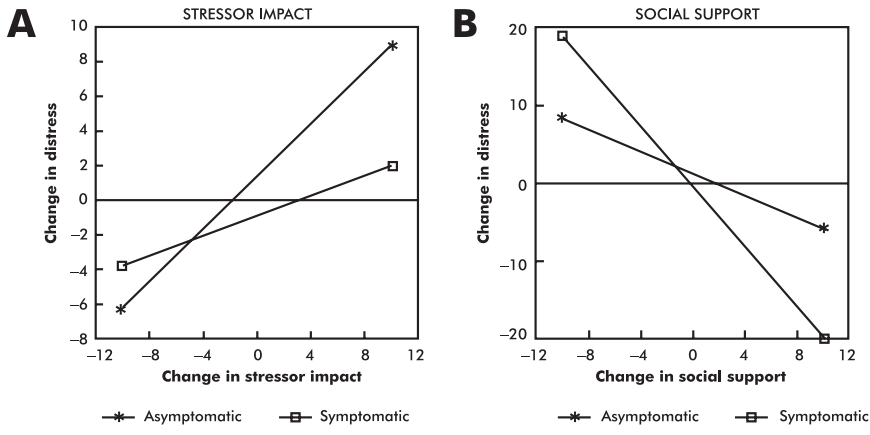

Figure 6–4. Relationship between changes in stressor impact and social support and change in psychological distress in a sample of men from the Natural History Cohort who were in either the asymptomatic or symptomatic stages of HIV-1 infection ($N = 367$ change scores across time periods). **(A)** *Psychological response to stressor impact.* The positive relationship between psychological distress and life stressor burden was strongest in the asymptomatic stage of HIV-1 infection. **(B)** *Psychological distress response to social support.* The inverse relationship between psychological distress and social support became stronger in the early symptomatic stage of HIV-1 infection.

Boyne and Arthur 1986; Chandra 1989; Fabris et al. 1988; Horrobin 1990; Irwin et al. 1990; Kiecolt-Glaser and Glaser 1988; Klein et al. 1988).

A multiple regression using all control variables with probability of $r_s \leq 0.20$ resulted in five independent predictors that were added to the psychosocial model analyses: 1) history of high levels of alcohol use, 2) retinol level, 3) cobalamin level, 4) omega-3 polyunsaturated fatty acids level, and 5) selenium intake. History of alcohol use had a negative relationship with NK cell cytotoxicity, as expected (Irwin et al. 1990). All of the nutritional parameters except selenium intake had a positive relationship with NK cell cytotoxicity. Selenium intake is a categorical variable indicating selenium supplementation and may be a surrogate marker for exces-

sive multivitamin and mineral supplementation, which has been associated with impairment of cellular immune functions (Beisel et al. 1981).

In this study, we found that coping style, and to a lesser extent life stressors and social support, were associated with NK cell cytotoxicity in asymptomatic HIV-1-seropositive homosexual men (Figure 6–5). These results extended to this and other immunologic outcomes from the prior work described earlier in this chapter based on the same SSC model predictors for determining associations with psychological distress (Blaney et al. 1991a). Three direct effects for NK cell cytotoxicity were found: 1) a positive association with active coping style ($P < 0.02$), 2) a trend toward a negative relationship with focusing on and venting of emotions ($P < 0.07$), and 3) a near trend toward, as expected, a negative association with life stressor impact ($P = 0.12$). Although no direct effects of social support on NK cell cytotoxicity were found, a nonsignificant trend toward an interaction between life stressor count and social supports suggested that social support buffered a deleterious effect of life stressor count at relatively low stressor levels. This trend is supported by previous research on psychological distress outcomes that demonstrated a buffering effect for social support on the impact of life stressors (Cohen and Wills 1985). The stressor-buffering effect of social support may be even more pronounced in circumstances in which the life stressor experienced is not only met by available social support (measured here) but also complemented by satisfaction with and sufficiency of the support provided.

It is important to note that post hoc analysis of the SSC model omitting the control variables did not show any significant effects on NK cell cytotoxicity. The inclusion of control variables that have an established or theoretical relationship with the outcome variable under investigation appears to be essential to gaining a clear picture of the true relationships in any particular sample.

In a subsequent cross-sectional analysis of the SSC model, we examined CD4 cell count, lymphocyte blastogenesis in response to the mitogen phytohemagglutinin, and NK cell cytotoxicity in asymptomatic HIV-1-seropositive ($n = 84$) and HIV-1-seronegative ($n = 44$) individuals (Goodkin et al. 1991). Our selection of control

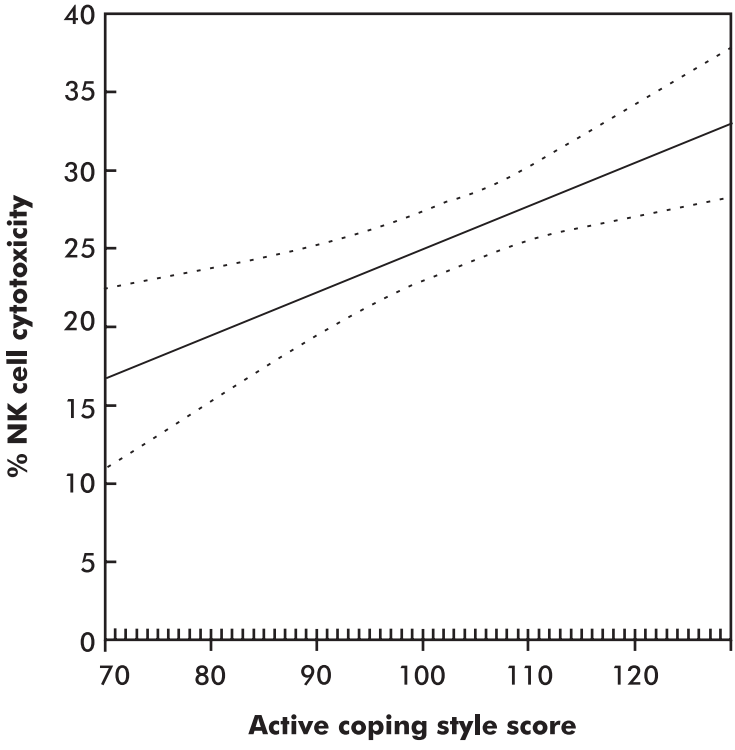

Figure 6–5. Relationship between coping style and natural killer [NK] cell cytotoxicity in a sample of asymptomatic HIV-1-seropositive individuals ($N = 62$) from the Natural History Cohort. Active coping style score was positively related to NK cell cytotoxicity. Dotted lines are the upper and lower bounds of the 95% confidence interval. ($P < 0.02$ for β weight in stepwise linear multiple regression analysis testing the SSC model with control variables.)
Source. Reprinted from *Journal of Psychosomatic Research,* Vol. 36, K. Goodkin, N. T. Blaney, D. Feaster, et al.: "Active Coping Style Is Associated With Natural Killer Cell Cytotoxicity in Asymptomatic HIV-1 Seropositive Homosexual Men," pp. 635–650. Copyright 1992, with permission from Elsevier Science.

variables was guided by the procedure described earlier, in the section on methodologic considerations. The final set of covariates for CD4 cell count included plasma vitamin C levels, red blood cell folate levels, and history of recreational substance use. For lymphocyte proliferative response to phytohemagglutinin, the control

variables were CD4 cell count, plasma vitamin E levels, and current recreational substance use. Finally, for NK cell cytotoxicity, the relevant control variables were plasma vitamin A level and alcohol history.

There was an inverse relationship between negative life stressors and CD4 cell count. For HIV-1-seronegative individuals the relationship was not only statistically significant but also strong, whereas for HIV-1-seropositive individuals the relationship was less strong and represented a trend only (Figure 6–6A). The range of CD4 cell count for HIV-1-seropositive individuals fell below that found in HIV-1-seronegative individuals. This raises the possibility that for the HIV-1-seropositive individuals, compared with HIV-1 seronegative individuals, there was a "floor effect" in the relationship between negative life stressors and CD4 cell count. In addition, the range of life stressor count was larger for the HIV-1-seropositive individuals than that for the HIV-1-seronegative individuals, an indication of the importance of focusing on life stressor impact in this patient population.

A similar pattern was observed for lymphocyte proliferative response to phytohemagglutinin, although the relationship between lymphocyte proliferative response to phytohemagglutinin and negative life stressor count was not statistically significant, perhaps because of the greater inherent variability in this immune measure (Figure 6–6B). Again, as expected, the range of lymphocyte proliferative response to phytohemagglutinin for HIV-1-seropositive individuals fell below that for HIV-1-seronegative individuals.

A significant inverse relationship was seen between negative life stressor count and NK cell cytotoxicity for HIV-1-seronegative individuals, whereas a direct, though nonsignificant, relationship was found for HIV-1-seropositive individuals (Figure 6–6C). On this measure, the values for HIV-1-seropositive and HIV-1-seronegative individuals fell within the same range. These effects for negative life stressors were observed in a model in which the other two domains in the SSC model (i.e., social support and coping style), as well as the specific control variables described earlier, were included.

In addition to the effects for negative life stressors, disengagement and denial had a strong negative effect, and active coping showed a trend toward a positive effect, on lymphocyte proliferative response

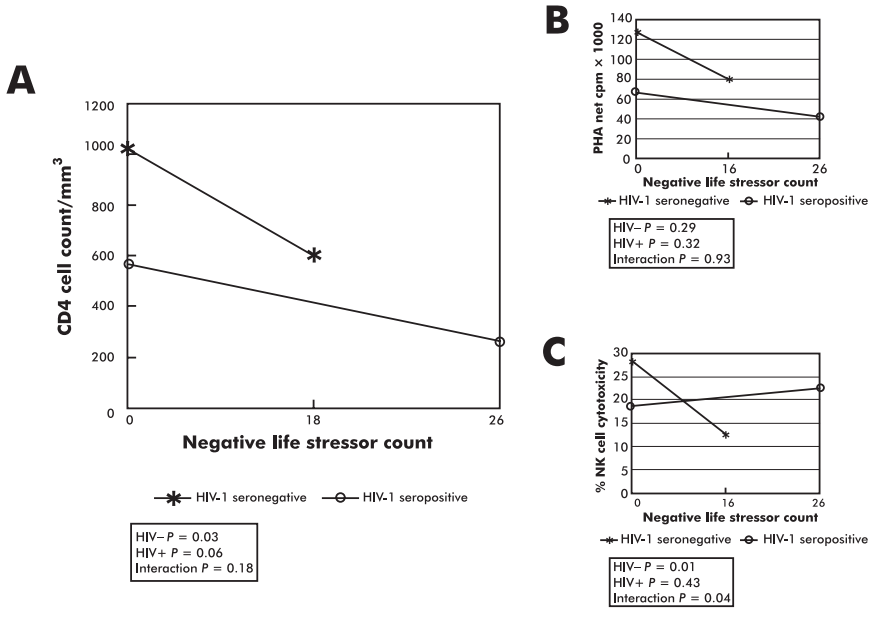

Figure 6–6. Relationship between immune parameters and life stressor count in a sample of asymptomatic HIV-1-seropositive (n = 84) and HIV-1-seronegative (n = 44) men from the Natural History Cohort. **(A)** *CD4 cell count by negative life stressor level and HIV-1 serostatus.* The number of life stressors was negatively related to the CD4 cell count. This negative relationship was strongest in the HIV-1-seronegative group. The range of life stressors was greater in the HIV-1-seropositive group. **(B)** *Lymphocyte proliferative response to phytohemagglutinin (PHA) response (net counts per minute, or cpm) by negative life stressor level and HIV-1 serostatus.* The pattern of results shown is similar to that for CD4 cell count, although the relationship between lymphocyte proliferative response to phytohemagglutinin and negative life stressor count was not statistically significant. **(C)** *Natural killer (NK) cell cytotoxicity by negative life stressor level and HIV-1 serostatus.* Negative life stressor counts were negatively associated with NK cell cytotoxicity in the HIV-1-seronegative group.

to phytohemagglutinin in the HIV-1-seronegative group. Focus on and venting of emotions showed a strong negative effect on NK cell cytotoxicity for the HIV-1-seronegative group and a trend toward

a negative effect for the HIV-1-seropositive group.

The effects for negative life stressors and coping style described above were in accordance with the theoretical expectations derived from the SSC model—that is, negative life stressors and passive, maladaptive dispositional coping styles (denial and disengagement/distraction and avoidance) have negative effects on cellular immune function. There were, however, a few results that did not conform to predictions based on our model. Whereas active coping showed a trend toward a positive relationship with lymphocyte proliferative response to phytohemagglutinin for the HIV-1-seronegative individuals, it showed a trend toward a negative relationship for the HIV-1-seropositive individuals. In addition, disengagement and denial showed a positive relationship with NK cell cytotoxicity for the HIV-1-seropositive individuals. Situational and HIV-1 specificity of coping strategy selection may account for these findings, since only dispositional, contextual coping measures were used. In addition, stressor controllability may moderate the effect of selected passive coping strategies on distress and immune outcomes. For example, focus on and venting of emotion may be adaptive in the setting of the uncontrollable and sudden loss of a partner due to death after a bout of *Pneumocystis carinii* pneumonia. However, this same strategy may be maladaptive when used with the controllable stressor of coping with denial of hospital payments from an insurance company due to a mistake in billing. Likewise, active coping strategies may be adaptive for such controllable stressors but maladaptive for uncontrollable stressors such as the loss itself. These divergent results on coping style are being addressed in current research that assesses situational as well as dispositional coping styles; stressor controllability matching with coping strategy and HIV-1-specific measures of stressor count and impact; social support availability, satisfaction, and sufficiency; and coping strategy selection.

Bereavement

The foregoing examinations of stressor, social support, and coping relationships with immune measures may, understandably, reflect

a design that is not maximal in terms of statistical power, since the stressors occured at different points over the prior 6 months and were of varying intensity. Bereavement is a single, potent, and, unfortunately, frequent stressor among individuals with HIV-1 infection (Martin 1988; Martin and Dean 1993; Neugebauer et al. 1992). This stressor has been shown to be associated with decrements in cellular immune function after loss of a spouse. In fact, decrements in lymphocyte proliferative response to phytohemagglutinin (Bartrop et al. 1977), as well as in NK cell cytotoxicity (Irwin et al. 1988), have been documented. Therefore, we reasoned that bereavement would be a stressor that might demonstrate effects independently of life stressors taken generally on these same immune measures and that a time-dependent relationship may be discerned.

To investigate this possibility further, we applied the SSC model and statistical analytic framework described earlier to bereavement (see Chapter 10, this volume, for expanded discussion of the immune responses associated with bereavement). From our natural history study, we used responses to bereavement-related questions on the Life Experience Survey—our modification of the Sarason et al. (1978) measure—which includes items for the loss of a close friend and, in our amended form for homosexual men, a lover rather than spouse (Goodkin 1989; Goodkin et al. 1992). In this analysis, we again included all of the SSC variables in the psychosocial predictor domains and control variables, but we added to the multiple regression analysis an indicator variable for experiencing a loss within the past 6 months. Our SSC model, comprising negative life stressors, social support, and coping style (Goodkin 1987, 1989, 1990b; Goodkin et al. 1993a, 1993b, 1996, 1998, 1999), was estimated on the basis of three specifications: 1) concurrently, with baseline values of psychosocial variables used to predict concurrent values of cellular immune measures; 2) prospectively, with baseline psychosocial variables used to predict six-month follow-up values of the immunologic measures; and 3) concurrently, with 6-month follow-up values of psychosocial values (and baseline bereavement) used to explain 6-month follow-up values of the immunologic variables.

The sample comprised 132 homosexual men, 83 of whom were HIV-1 seropositive and asymptomatic, and 49 of whom were HIV-1 seronegative. Twenty-eight had experienced the death of a close friend or lover within 6 months of entering the natural history study. The relevant control variables were 1) history of excessive alcohol use for both NK cell cytotoxicity and lymphocyte proliferative response to phytohemagglutinin and 2) plasma zinc level for lymphocyte proliferative response to phytohemagglutinin.

Bereavement was found to have a negative effect on both NK cell cytotoxicity and lymphocyte proliferation in response to phytohemagglutinin. Active coping style was associated with higher levels of both immune measures. Among the NK cell cytotoxicity models, the specifications included, in addition to all of the main effects mentioned earlier, bereavement interactions with background life stressors, social support, and active coping style and an indicator variable for HIV-1 serostatus. Among the models that involve lymphocyte proliferative response to phytohemagglutinin, there was extreme heteroscedasticity by HIV-1 serostatus. This finding, coupled with our prior research showing differences in these relationships by serostatus, precluded the inclusion of data for HIV-1-seronegative individuals. Because of the decreased sample size, interaction effects were not tested for this variable.

The results for NK cell cytotoxicity showed that in all three specifications—the baseline concurrent model, the prospective model, and the concurrent 6-month follow-up model—the overall model (including controls) was significant at $P < 0.0001$. All three specifications showed a negative effect of bereavement and a positive effect of active coping on NK cell cytotoxicity. Both the concurrent baseline and baseline–six-month follow-up specifications showed a negative effect of focusing on and venting of emotions. (The concurrent specification at 6 months showed a trend toward this relationship.) The baseline concurrent model showed the effect of active coping on NK cell cytotoxicity to be stronger for bereaved individuals, though the bereaved and nonbereaved groups were not significantly different in this regard. In the prospective specification, social support was seen to be significantly positively related

to NK cell cytotoxicity for the bereaved only.

The three overall model specifications for lymphocyte proliferative responses to PHA were significant at $P < 0.05$, $P < 0.03$, and $P < 0.008$, respectively. The results for the baseline concurrent model were driven by two control variables: the predicted negative effect of history of alcohol use and the positive effect of plasma zinc level. The prospective model (baseline to 6 months) showed a negative effect of bereavement, a positive effect of active coping, and a trend toward a negative effect of focusing on and venting of emotions. The concurrent 6-month follow-up model specification showed a negative effect of background life stressors (though not bereavement) and a positive effect of active coping style. An unexpected negative effect of concurrent social support was found as well; this effect may be moderated by lack of satisfaction with or insufficiency of social support (parameters to be measured in future studies).

In sum, the results indicate that bereavement has deleterious effects on two cellular immune measures: NK cell cytotoxicity and lymphocyte proliferative response to phytohemagglutinin. The latter may be important for clinical reasons, because it is related to the function of T lymphocytes, which is decreased with progression of HIV-1 infection. The former may be clinically important as well, especially for patients in the later stages of disease, since NK cell cytotoxicity is relatively well preserved compared with CD4 cell count and its function may overlap with protection against illnesses also conferred by CD4 lymphocytes. In addition, the results suggest that provision of social support at the time of a loss is important in order to prevent later decrement in NK cell cytotoxicity (in our study, 6 months later). They also suggest that active coping style should be supported (perhaps, specifically with controllable stressors attending loss) so that levels of both NK cell cytotoxicity and lymphocyte proliferative response to phytohemagglutinin might be preserved over the year after loss. Likewise, the impact of background life stressors (in our study, seen on lymphocyte proliferative response to phytohemagglutinin 6 months after the loss) could be diminished by a stress management format incorporated into a bereavement support group intervention technique.

Longitudinal Analysis of Progression of HIV-1 Infection

A longitudinal analysis of the final HIV-1-seropositive cohort was conducted; the sample included 102 individuals for whom data from multiple time points were available (Goodkin et al. 1993c). This investigation included CD4 cell count, β_2-microglobulin levels, and psychological distress as the outcome measures. It should be noted here that β_2-microglobulin level is a laboratory marker indicator of HIV-1 progression that is independent of the CD4 cell count and is a known indicator of abnormal immunologic activation as well as of the extent of lymphocyte cell death. Unlike the CD4 cell count, β_2-microglobulin levels increase, rather than decrease, with disease progression. The SSC model variables—life stressors, social support, and coping style—were used as the hypothesized predictors. CDC staging at baseline, prescribed medication use, nutritional status (plasma levels of vitamins B_6 and B_{12} and zinc), and lifestyle factors (e.g., recreational substance use; alcohol consumption, current and past; and smoking, current and lifetime exposure in pack-years) were used as control variables. Hematocrit levels were also planned for inclusion in these analyses of HIV-1 laboratory progression markers, but because of the restricted range found (i.e., nearly all values were within the normal range), this laboratory progression marker was not included. The restricted range of hematocrit levels is not surprising, since hematocrit is a known indicator of HIV-1 progression specific to late-stage disease (i.e., AIDS) (Justice et al. 1989).

A separate linear trend was fitted to each of the aforementioned measures for each individual in the sample, a process that resulted in an estimated intercept and slope for each individual (and each measure). The value of the estimated intercept is the predicted initial value of that measure for a particular individual. The value of the estimated slope is the predicted (6-month) change in the measure for that individual. Use of this measure of change is likely to be more reliable than use of observed 6-month change scores. The linear trend fitted the data adequately. Correlations between true initial values and predicted initial values (the estimated intercept) ranged from 0.89 to 0.96.

These predicted values were then used in six (second-order) regression analyses in which the predicted intercepts and slopes of CD4 cell count, β_2-microglobulin level, and psychological distress were the dependent measures. For the three regressions on predicted initial values, the independent variables were the predicted initial values of the model indicators (life stressor count, social support, and coping style measures). For the three regressions on predicted 6-month change (slopes), the independent measures were the predicted 6-month changes in the same set of model predictor variables. In addition, the predicted initial value of the dependent measure was included as a control for baseline levels.

The results of these regression analyses indicate that stressful life events are inversely related to CD4 cell count over time both for the predicted initial level (Figure 6–7A) and for long-term change (Figure 6–7C) such that increasing number of life stressors is associated with sharper decreases in CD4 cell counts, both when control variables are included and when they are absent. The results also support a positive relationship between active coping style and CD4 cell count when the predicted initial value was used but no controls were included (Figure 6–7B). Although this active coping style association was not found when predicted change in values was used, two passive coping styles—focus on and venting of emotions and turning to religion—were negatively associated with predicted change in CD4 cell count, both with and without control variables, as predicted by the model. Thus, both the active and passive components of our coping style hypothesis received support across the analyses we conducted, and the salutary effects of active coping style also seemed to be correlated with at least some of the control variables used.

As was predicted, active coping style was significantly and negatively associated with predicted initial β_2-microglobulin level with and without control variables (Figure 6–8). In addition, there was a positive relationship between life stressors and predicted initial β_2-microglobulin level when controls were included in the model. One passive coping style was found to be positively associated with predicted initial β_2-microglobulin level—focus on and venting of emotions—although there was only a trend for such an

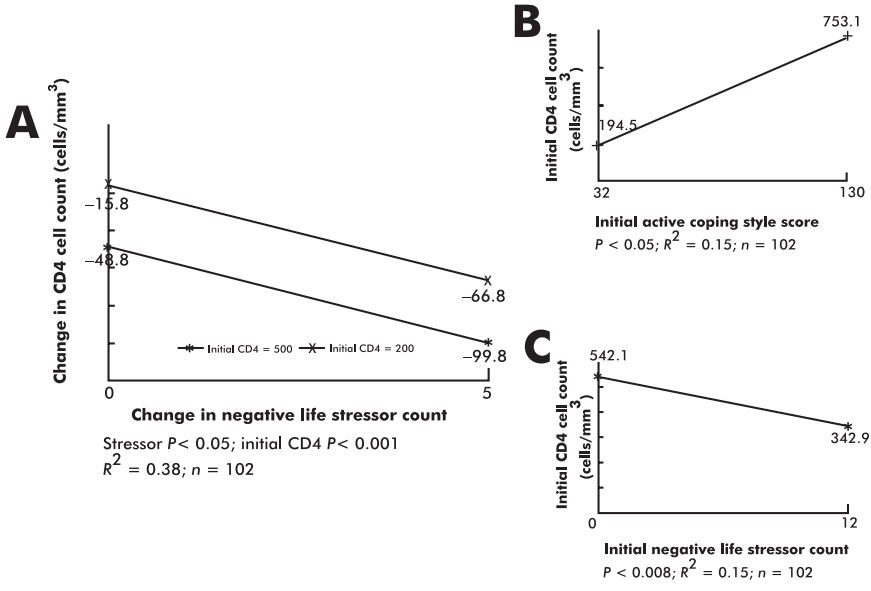

Figure 6–7. Relationship between outcome measures and Stressor-Support-Coping model variables in a longitudinal multiple regression analysis of a sample of HIV-1-seropositive men (N = 102) from the Natural History Cohort. **(A)** *Six-month change in CD4 cell count predicted by change in negative life stressor count.* Increases in life stressors were associated with decreases in CD4 cell count. These decreases were largest for higher levels of CD4 cell count, a finding that suggests the possibility of a "floor effect" (two levels are provided for illustration). **(B)** *Initial CD4 cell count as a function of active coping style score.* Initial CD4 cell count was positively related to initial level of active coping style score. **(C)** *Initial CD4 cell count as a function of negative life stressor count.* Initial CD4 cell count was associated with initial life stressor count.

association. No relationships were observed, however, when the predicted change in value of β_2-microglobulin level was used. The absence of any relationship may have been the result of the small variability in β_2-microglobulin level over time.

The hypothesis that the foregoing results are related to psychological distress is supported by the analysis of negative life stressors and coping style measures for prediction of initial level and

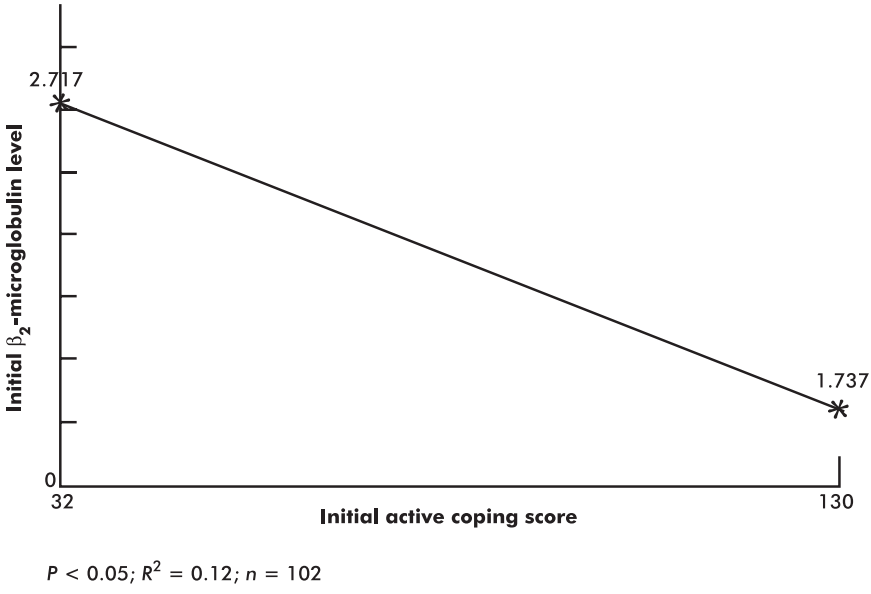

Figure 6–8. Relationship between active coping style and initial β_2-microglobulin level (μg/L) in a longitudinal multiple regression analysis of a sample of HIV-1-seropositive men ($N = 102$) from the Natural History Cohort. Initial active coping style score was negatively related to the initial β_2-microglobulin level.

6-month change in levels of psychological distress. Stressful life events with a negative impact were associated with higher levels of psychological distress in both predictive methods (Figure 6–9A, B). Active coping style was negatively associated with psychological distress level, whereas passive coping styles (disengagement and denial, focus on and venting of emotions), as expected, were positively associated with psychological distress level (Figure 6–9C, D). However, turning to religion showed no significant association with psychological distress level in these analyses. Further, the associations with coping styles were not supported in the analysis when predicted changes in psychological distress levels were considered.

Overall, the results support a contribution of our predictive model of life stressors, social support availability, and coping style to variance in laboratory progression markers of clinical progres-

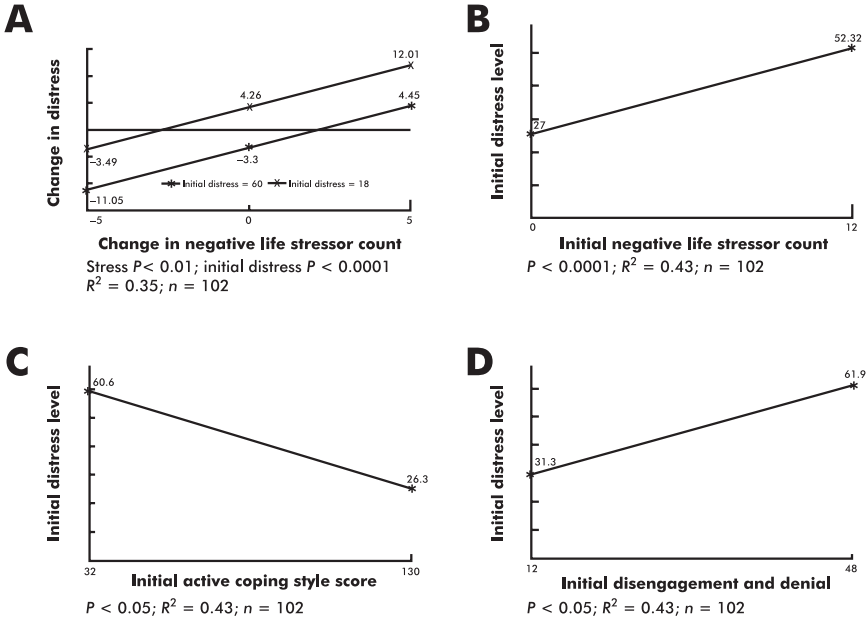

Figure 6–9. Relationship between negative life stressors/coping style measures and initial level and 6-month change in levels of psychological distress in a longitudinal analysis of a sample of HIV-1-seropositive men ($N = 102$) from the Natural History Cohort. **(A)** *Six-month change in psychological distress predicted by change in life stressor count.* An increase in life stressor count was associated with an increase in psychological distress. The amount of increase was highest at lower levels of psychological distress. Decreases are largest for higher levels of psychological distress (two levels are provided for illustration). **(B)** *Initial psychological distress as a function of negative life stressor count.* Initial psychological distress was positively related to initial negative life stressor count. **(C)** *Initial psychological distress as a function of initial active coping style.* Initial psychological distress was negatively related to initial active coping style score. **(D)** *Initial psychological distress as a function of disengagement and denial.* Initial psychological distress was positively related to initial disengagement and denial.

sion of HIV-1 infection (CD4 cell count, β_2-microglobulin level), at least in the asymptomatic and early symptomatic stages of disease. It should be pointed out that other known laboratory progression markers of HIV-1 infection—free p24 core antigen level and total binding capacity, HIV-1-specific cytotoxic T lymphocyte count and function, neopterin level, Th1 and Th2 cytokine levels, and viral load—remain to be investigated within this theoretical model to extend and confirm such relationships. Nevertheless, two of our theoretically based predictors—life stressors and coping style—were related to the CD4 cell count and β_2-microglobulin level, two of the most commonly used progression markers. High levels of negatively rated life stressors and passive coping style consistently predicted deleterious relationships, whereas active coping style demonstrated salutary relationships. It should be noted that social support availability, although important in relation to psychological distress, did not show significant relationships with the laboratory progression markers analyzed here. Possible additional measures related to social support, such as the larger network or organizational level, might differentially contribute to these effects in future studies.

The relationships observed here between psychosocial factors and laboratory progression markers may be mediated by psychological distress, or they may represent direct effects on immune measures, or a combination of these two types of relationships may hold. The nature of these relationships will be investigated in future studies involving path analytic modeling strategies with linear structural equations.

Physical Health

Using a prospective design with the SSC model, we sought to determine the influence of psychosocial factors on health status in early HIV-1 infection (Blaney et al. 1992; Goodkin et al. 1996, 1998; see also Chapter 10, this volume). The sample for this analysis comprised 90 HIV-1-seropositive homosexual men, 68 of whom were asymptomatic (1993 CDC stage A) and 22 of whom were symptomatic (1993 CDC stage B). The measures were obtained at entry

(time 1) and 6 months later (time 2). Psychosocial predictors (time 1) included life stressor count, perceived available social support, and four dispositional coping styles. Health status (time 2) consisted of the total number of clinical symptoms experienced over the prior 6 month interval as assessed by a medical history and a complete physical examination. The medical history involved a systematic review of all symptoms across major body systems as well as symptoms specifically referable to HIV-1. The physical examination involved noting HIV-1-specific signs as well as any other clinically observable abnormalities. Control variables included 1993 CDC stage, nutritional status, neurocognitive function, CD4 lymphocyte count, and prior physical symptom levels.

Life stressor count and active coping style prospectively and independently predicted number of physical symptoms over a 6-month period (Figure 6–10). As expected, higher life stressor counts were associated with more physical symptoms (Figure 6–10A), and higher frequency of active coping style was associated with fewer physical symptoms (Figure 6–10B). These associations remained after control for prior physical symptom level. In a post hoc exploratory analysis, we examined the differences in these results, controlling for 1993 CDC stage. The model was estimated separately for the 68 asymptomatic and 22 symptomatic subjects. Because of the limited sample size, these comparisons need to be interpreted as preliminary. However, there was evidence that the life stressor count effect in the two groups was very similar, whereas the active coping style effect was stronger in the symptomatic subjects. Although at every given active coping style level, the symptomatic individuals had more physical symptoms than did the asymptomatic individuals, the difference in symptoms between groups was smaller when the level of active coping style was greater. These findings suggest that our theoretical psychosocial model predictors, particularly life stressor count and active coping style, deserve serious consideration in clinical screening and in the development of prophylactic intervention strategies to enhance the physical health of individuals with HIV-1 infection.

Conclusion

The evidence from the natural history study described in this chapter indicates that there are important relationships between the SSC model representing the three theoretical psychosocial predictor domains—life stressor burden, social support availability, and dispositional coping style—and the three outcome domains—psychological well-being, immunologic function, and physical health—among HIV-1-infected individuals. These results were obtained by means of a multivariable methodology—multiple regression analysis—that controls for the levels of all predictors included. In addition, potential control variables were assessed in a consistent fashion and included, where indicated, in the final

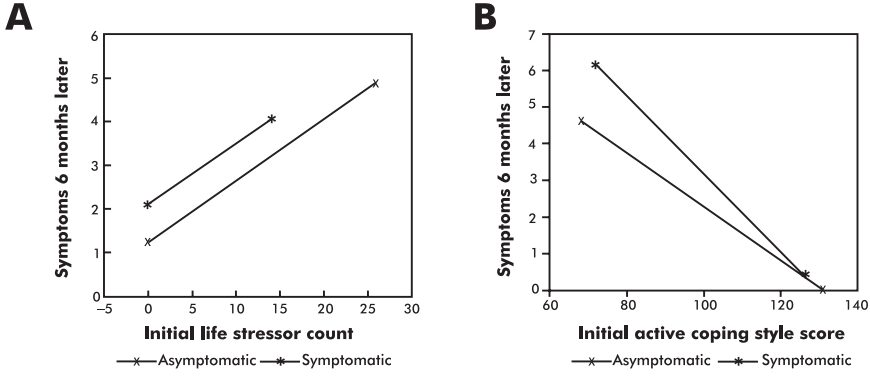

Figure 6–10. Relationship between life stressor count and active coping style in a sample of asymptomatic (n = 68) and symptomatic (n = 22) HIV-1-seropositive men from the Natural History Cohort. **(A)** *Physical symptom response to initial life stressor count.* Initial life stressor count was positively related to physical symptoms 6 months later. The relationship was essentially the same for the asymptomatic and symptomatic groups, with the number of physical symptoms for the symptomatic group elevated, relative to that in the asymptomatic group, at all levels of life stressors. **(B)** *Physical symptom response to initial active coping style.* Initial active coping style score was negatively related to physical symptoms 6 months later. This relationship was stronger for the symptomatic group.

model tests. In some cases, control variable inclusion uncovered significant differences that otherwise would not have been observed for psychosocial factors and immunologic measures; this confirms the need for analysis based on a contextual psychosocial model rather than multiple tests of correlations of single psychosocial variables.

The evidence indicates that life stressor levels, social support availability, and dispositional coping styles (both active and passive) contribute to the level of psychosocial distress in this patient population. There is some indication that in the early symptomatic stage of HIV-1 infection, stressor levels become less important and social support availability becomes more important in relation to psychological distress.

In the immunologic domain, life stressor counts and active coping style appear to be of substantial import. There is some indication that life stressor counts are less strongly related to immune measures in HIV-1-infected individuals than in individuals at risk for this infection. This should not be surprising, however, since HIV-1 infection directly affects the immune system itself and possibly renders that system less responsive to changes related to psychosocial as well as other factors normally affecting immune responses. Moreover, the presence of a single, potent stressor—bereavement—demonstrated significant immunologic effects on both NK cell cytotoxicity and lymphocyte proliferative responses to phytohemagglutinin in those infected with HIV-1. An active coping style was important in the prediction of NK cell cytotoxicity and lymphocyte proliferative response to phytohemagglutinin in the setting of bereavement, as well as in the prediction of two laboratory progression markers of HIV-1 infection generally (CD4 cell count and β_2-microglobulin level).

In the realm of physical health, the evidence indicates a role for the same predictors that were related to immunologic measures (life stressor counts and dispositional active coping style), with the role of active coping style potentially becoming even more clinically relevant in the early symptomatic stage of HIV-1 infection, though future studies should also focus on later stages of disease.

Some evidence suggests that supportive therapy and emphasis on active coping strategies may be even more important for the symptomatic HIV-1-seropositive individual than for the asymptomatic HIV-1-seropositive individual. Clearly, such interventions will have direct, if not immediate, effects on the quality of life of the HIV-1-infected individual to the extent that they reduce psychological distress. As well, there is reason to believe that, over time, these types of interventions will have effects on immune function and physical health.

Although, as the results from this cohort indicate, psychosocial factors play a role in HIV-1 infection, there are mixed results from one specification to another and differences from one immune parameter to another. There are also differences between data from the cross-sectional and longitudinal analyses. Several more recent extensions to the psychosocial model may illuminate the reasons for these differences. First, the SSC model, as originally described (Goodkin 1990b; Goodkin et al. 1993a, 1993b), includes stressors, along with the parameters of predictability, controllability, and duration. The data from the natural history cohort reported here do not include information on these parameters. This information would allow better matching of the type of stressors experienced with the appropriate coping style. Although we generally view passive coping styles as maladaptive, in the case of uncontrollable stressors certain types of passive coping (e.g., venting of emotions or turning to religion or spirituality) may be the most appropriate response. Likewise, in the investigations reported here, we used assessments of coping as a disposition. Assessment of situational coping strategy would allow better contextual matching between life stressors and coping. Such matching is of particular importance in investigations of specific stressors such as bereavement.

Finally, the use of standardized (contextual) stressor surveys may exclude some important details specific to the disease under study. In HIV-1 infection, an assessment of stressors, social support, and coping efforts specific to HIV-1 may help to explain variance in the immune function and physical health of individuals with HIV-1 infection. Such an assessment is currently being done in our ongoing bereavement support group intervention study for

HIV-1-seropositive and at-risk homosexual men (see Chapter 10, this volume).

On balance, the results from the study of the longitudinal psychoneuroimmunologic relationships in HIV-1 infection at this time lend added importance to the role of behavioral interventions in the treatment of individuals with this infection. Regarding psychological distress, these results may be used to target prophylactic behavioral interventions to individuals with high levels of life stressors, low levels of social support availability, low levels of active coping styles, and high levels of passive coping styles. Moreover, specific interventions are suggested by each of these factors. Supportive group therapy is suggested for low social support availability and in the specific setting of HIV-1-associated bereavement and multiple loss (as in the bereavement support group intervention study described in Chapter 10). Low use of active coping style and high use of passive coping style would be an indication for cognitive-behavioral therapy aimed at changing cognitions about coping strategy selection in the face of confrontation by life stressors. High life stressor count alone may be considered an indication for stressor management techniques involving deep muscular relaxation training, self-hypnosis, meditation, biofeedback, and/or other such techniques. This type of behavioral prophylactic strategy has a parallel in the primary medical care of patients with HIV-1 infection. With these patients, prophylactic treatments of lethal complications of HIV-1—for example, trimethoprim/sulfamethoxazole for *Pneumocystis carinii* pneumonia, fluconazole for cryptococcal meningitis, and rifabutin for *Mycobacterium avium-intracellulare* infection—have been well demonstrated and widely utilized.

Perhaps, in the future, prophylactic behavioral interventions for psychological distress, immunologic support, and deterrence of clinical progression should be considered to dovetail with primary medical prophylaxis. Such an approach would allow the optimum treatment of the patient by emphasizing the active role of the patient in the doctor-patient relationship as well as incorporating the most current advances in primary medical HIV-1-related treatment strategies prescribed by the physician. Such comprehensive

treatment built on mutual participation would represent a true clinical application of the biopsychosocial model of health and disease in HIV/AIDS and may prove useful in the treatment of a number of chronic illnesses.

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Chapter 7

Cognitive Function in HIV-1 Infection

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Human immunodeficiency virus type 1 (HIV-1) infection is frequently accompanied by neurological complications, including cognitive disorders. Evidence of HIV-1 infection in the brain can be found throughout the course of infection and may first be detectable at or about the time of seroconversion. Minor cognitive impairments—those not significantly interfering with the ability to work or carry out daily activities—have been reported at all stages of HIV-1 infection. A disabling dementing state most commonly occurs in the late stages of AIDS, but it can be the first presenting symptom of AIDS in some individuals. The clinical characteristics of HIV-1-associated dementia (HAD) (formerly referred to as AIDS dementia complex [ADC]) include abnormalities in memory and concentration and a slowing in the speed of processing information.One focus of this chapter is the various definitions of dementia in HIV-1 infection, which differ in terms of the specific cognitive processes that must be impaired as well as the specification that motor and/or behavioral abnormalities must

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occur in conjunction with these cognitive abnormalities[1].

In this chapter, we describe findings on minor as well as severe cognitive changes associated with HIV-1 infection. At this time it is not known whether minor cognitive changes associated with HIV-1 infection will develop into a dementing illness. The precise incidence of HIV-1-associated cognitive changes is unknown, in part because of methodologic differences among studies investigating such changes. Possible explanations for the discrepant findings in this area are presented. The concerns that anti-HIV-1 antibody–seropositive (hereafter referred to as HIV-1-seropositive) individuals may differ from one another in qualitative respects and that their scores on cognitive tests may not reflect the actual effects of HIV-1 infection on cognition are also addressed. Cognitive performance is modulated by attentional mechanisms that can be influenced by arousal levels, including anxious and depressive mood symptoms as well as fatigue and pain, all of which are common over the course of this infection. We distinguish between primary cognitive disorders associated with the effects of HIV-1 itself and the cognitive effects secondary to 1) complications of the associated immunosuppression (including opportunistic infections, tumors), 2) metabolic encephalopathies and delirium, and 3) iatrogenic effects (e.g., toxic responses to prescribed medications).

In this chapter, we begin with a summary of the clinical characteristics of HIV-1-associated cognitive disorders and a discussion of the diagnostic issues related to the various definitions of these disorders. We also detail the prevalence of these disorders and outline the risk factors for their development. We then address the cognitive assessment of HIV-1 (by domain of function) and the functional status assessment for HIV-1-associated cognitive disorders, as well as the need to exclude confounding factors in the diagnosis. We conclude with a discussion of how these disorders may be involved in the mediation of psychoneuroimmunologic effects in this population.

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[1]We use the term *HIV-1-associated dementia,* or HAD, rather than HIV-1-associated dementia complex because patients with HAD frequently present with accompanying behavioral or motor dysfunction but not necessarily both behavioral and motor symptoms (i.e., the complex).

HIV-1-Associated Cognitive Disorders

Clinical Characteristics

Cognitive disorders associated with HIV-1 infection range in severity from subclinical alterations in cognitive efficiency to severe dementing illness. The clinical features, incidence, and natural history of this dementia were first described by Navia and colleagues (1986b) in patients during the late stage of HIV-1 infection as an AIDS dementia complex consisting of cognitive, motor, and behavioral changes.

The initial clinical manifestations of HAD, in large part, suggest a subcortical brain process characterized by complaints of impaired concentration, memory loss, and mental slowing, as well as apathy and inertia. The increasing apathy, social withdrawal, and mental slowing are frequently mistaken for depressive symptoms or a major depressive disorder. Psychomotor slowing is frequently present, along with ataxia and incoordination. In some cases, these early clinical symptoms progress to a more pervasive and severe dementia within as short a period as 6 months.

The late manifestations of HAD include severe cognitive dysfunction, confusion, psychomotor slowing with long verbal response delays, and near or absolute mutism with a vacant stare. At the same time, motor signs and symptoms progress to frank weakness and general hypokinesia (Navia et al. 1986b). Neuropsychological (Becker et al. 1995; Janssen et al. 1989; Miller et al. 1990; Peavy et al. 1994) and neuroimaging evidence (Rottenberg et al. 1987) suggests that in the late stages of dementia in HIV-1 infection, subcortical as well as cortical brain structures are affected. Late-stage HAD is associated with a poor prognosis, with a median survival time of approximately 6 months (Day et al. 1992; McArthur et al. 1993; Navia et al. 1986a).

There is evidence that the foregoing clinical features of dementia are specific to pathophysiological changes induced by HIV-1 infection rather than to secondary opportunistic infections of the brain (e.g., cytomegalovirus infection), tumors (e.g., primary central nervous system [CNS] lymphoma), or metabolic encephalopathies

related to pulmonary, hepatic, or renal sources (McArthur 1994; Navia et al. 1986b).

This progressive and disabling dementia has been most frequently referred to as *AIDS dementia complex,* or ADC (Maruff et al. 1994; Navia et al. 1986b), but it has also been termed *subacute encephalitis* (Snider et al. 1983), *subacute encephalopathy* (Britton and Miller 1984), and, more recently, *HIV-1-associated dementia,* or HAD, by the American Academy of Neurology AIDS Task Force (American Academy of Neurology 1991). Although dementia in HIV-1 infection generally occurs during the late stages of the disease, it can be the first presenting symptom of AIDS—that is, HAD is AIDS-defining (Centers for Disease Control 1987).

HAD has been categorized as mild, moderate, or severe in terms of functional status, with the use of this diagnostic term having been expanded to considerably milder ranges of dysfunction in activities of daily living than had been applied hitherto. For this reason, as noted earlier, the term HIV-1-associated dementia is used in this chapter.

Changes in cognition not severe enough to be considered a dementia have also been observed in HIV-1-seropositive individuals at all stages of infection. During the past decade, considerable neuropsychological research has characterized the nature of HIV-1-associated cognitive changes. Attention, performance on speeded cognitive tasks, motor ability, and specific memory processes appear to be most sensitive to the effects of HIV-1 infection, although wide individual differences are observed.

Definitions

Attempts to better define the terminology and multiple manifestations of dementia, as well as minor cognitive changes, in HIV-1 infection have been made by a number of groups, including the AIDS Task Force of the American Academy of Neurology (1991); the American Psychiatric Association, in DSM-IV (American Psychiatric Association 1994); Atkinson, Martin, and Grant (Atkinson and Grant 1994; A. Martin and Grant 1994); and Becker and colleagues (1994).

The various sets of diagnostic criteria proposed for HAD have similarities as well as differences. Therefore, it is important that clinicians and investigators indicate the criteria used in diagnosing HAD. All four of the sets of diagnostic criteria for HAD require that there be 1) significant cognitive impairment in two different domains for at least 1 month and 2) impairment in the ability to work or perform social activities of sufficient severity to affect activities of daily living. Dementia is distinguished diagnostically from a delirium (e.g., on the basis of clouding of consciousness). However, dementia represents a risk factor for the occurrence of delirium. The occurrence of a delirium in the face of an ongoing dementia warrants both diagnoses. By definition, HAD is a diagnosis of exclusion; it cannot be made in the presence of CNS infections, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, metabolic encephalopathy, psychoneurotoxicity due to prescribed medications or to alcohol or recreational substance intoxication, withdrawal, or toxicity compatible with CNS disorder that might account for the observed cognitive deficits.

The four sets of diagnostic criteria for HAD differ in two areas: 1) the domains of cognitive function in which deficits must occur in order to be viewed as a dementia, and 2) the requirement that behavioral and/or motor abnormalities be present in combination with cognitive impairment.

Domains of Cognitive Impairment

Three of the sets of criteria for HAD (American Academy of Neurology 1991; Atkinson and Grant 1994; Becker et al. 1994; Martin and Grant 1994) require cognitive impairment in any two different cognitive domains measuring attention/concentration, speed of information processing, memory, perceptual processes, abstraction, or language processes. Only the dementia criteria for HAD proposed by Becker and colleagues (1994) operationally define the magnitude of cognitive impairment: the fifth percentile of the age-, education-, and culture-appropriate normative sample. The two-domain criterion takes into account the heterogeneity in patterns of cognitive impairment frequently observed in HIV-1 infection.

In contrast, the DSM-IV criteria require multiple cognitive deficits manifested by both memory impairment and one or more cognitive disturbances involving aphasia, apraxia, agnosia, or disturbance in executive functions, such as planning, organizing, abstracting, or sequencing. The DSM-IV diagnostic criteria do not distinguish among the dementias (e.g., Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, HAD) with respect to the areas of cognitive impairment required for a diagnosis. It is not clear how the DSM-IV diagnostic criteria for dementia, with their requirement of memory impairment, will influence the diagnosis of dementia in patients with HIV-1 infection.

In contrast to the severe verbal memory deficits observed in patients with Alzheimer's disease, memory impairment—especially verbal memory loss—is not the primary presenting symptom in patients with HIV-1 infection (Becker et al. 1994; Peavy et al. 1994) (see section on cognitive assessment later in this chapter). Indeed, the cognitive symptoms described in HIV-1 infection have been described in patients with Huntington's chorea, which is viewed as a prototypical subcortical dementia and the symptoms of which are easily distinguished from the aphasia, alexia, agnosia, and severe amnesia associated with the "cortical dementias" (e.g., Alzheimer's disease) (Cummings 1993; Peavy et al. 1994). However, it should be pointed out that the motor symptoms associated with Huntington's chorea (i.e., choreoathetoid movements) are not like those associated with HIV-1 infection, which are more similar to parkinsonian motor symptoms (i.e., bradykinesia, impaired manual dexterity, postural instability, ataxia, increased rigidity, masked facies, slowed saccadic eye movements, and sometimes tremor). Nonetheless, the cognitive symptoms associated with Parkinson's disease (i.e., those related to substantia nigra degeneration) do not appear to provide as close of a match to HIV-1-associated neurocognitive impairment as do the cognitive symptoms associated with Huntington's chorea (i.e., those related to caudate nucleus degeneration). Perhaps, the fact that HAD—an infectious process—affects both the caudate nucleus and the substantia nigra accounts for this divergence between the cognitive and motor symptom parallels with specific types of degenerative subcortical disease.

Behavioral and Motor Abnormalities

Of the four definitions of HAD, only the set of criteria proposed by the American Academy of Neurology AIDS Task Force (1991) requires that cognitive impairment be in combination with at least one of the following: 1) acquired abnormality in motor functioning and 2) decline in motivation or emotional control or change in social behavior. In contrast, the set of criteria for dementia proposed by Becker et al. (1994) specifies cognitive impairment in two different cognitive domains or cognitive impairment in one domain along with personality and/or behavioral change (e.g., violent or aggressive behavior, hallucinations, delusions, or other signs of neuropsychiatric disturbance). According to Becker et al. (1994), motor deficits do not play a role in the diagnosis of HAD despite the fact that motor dysfunction frequently occurs with CNS manifestations of HIV-1. Motor dysfunction does affect neuropsychological test performance; however, it is frequently possible to disentangle the confounding effects of motor deficits from cognitive test performance in HIV-1 infection (Becker et al. 1994; Miller and Wilkie 1994; Wilkie et al. 1990, 1992) as well as in other diseases, such as Parkinson's disease (Sagar 1991).

Three of the aforementioned groups also describe a minor cognitive impairment associated with HIV-1 infection. This condition is referred to by the American Academy of Neurology AIDS Task Force (1991) as *HIV-1-associated minor cognitive/motor disorder* (MCMD) and by Atkinson, Martin, and Grant (Atkinson and Grant 1994; Martin and Grant 1994) as an *HIV-1-associated mild neurocognitive disorder.* In an addendum to DSM-IV (American Psychiatric Association 1994), mild neurocognitive disorder is described as a condition requiring further research before it may be considered a formal DSM diagnostic category. These three sets of criteria share the requirement that mild cognitive impairment must occur in at least two different cognitive domains, including attention/concentration, information processing speed, memory, motor skills, and perceptual-motor performance. In addition, DSM-IV and Atkinson, Martin, and Grant list two additional cognitive domains (abstraction and language) that may be affected.

Three of the four sets of criteria for HAD specify that the cognitive deficits must be verified by neuropsychological testing, with the American Academy of Neurology AIDS Task Force (1991) also requiring verification by neurological examination. Atkinson and Grant (1994) propose that the degree of impairment be 0.5 standard deviations or more below that of the age- and education- appropriate normative group. The American Academy of Neurology AIDS Task Force and Atkinson et al. criteria specify that the cognitive impairment must be present for at least 1 month (American Academy of Neurology 1991; Atkinson and Grant 1994; cf. Martin and Grant 1994), whereas DSM-IV recommends that the cognitive impairment be present for at least 2 weeks (American Psychiatric Association 1994).

All four groups recognize that this minor cognitive disorder will be accompanied by some degree of impaired functional ability, with the functional impairment described as either mild (American Psychiatric Association 1994; Grant and Atkinson 1994) or apparent only in the most demanding aspects of activities of daily living (American Academy of Neurology 1991). In contrast, the magnitude of functional impairment required for a *dementia* varies among the criteria sets, specified as marked (Atkinson and Grant 1994), significant (American Psychiatric Association 1994), or sufficient to cause at least mild impairment in activities of daily living (American Academy of Neurology 1991). HAD as defined by the American Academy of Neurology AIDS Task Force criteria would be a much more common diagnosis than in the past, when this diagnosis was typically reserved only for individuals with the most severe impairment in activities of daily living. Obviously, further research is needed in order to better define the magnitude of the functional impairment associated with varying degrees of cognitive impairment in HIV-1 infection.

It may be more difficult to follow the course of cognitive impairment in HIV-1 infection when one uses the DSM-IV criteria rather than one of the other three criteria sets. In DSM-IV, the criteria for mild neurocognitive disorder allow cognitive impairment to occur in any two of seven domains (attention/concentration, information processing speed, memory, language, abstraction, perceptual

skills, and motor skills), whereas the criteria for dementia require memory loss along with either aphasia, apraxia, agnosia, or disturbance in executive functioning. Hence, if no memory impairment is present, the person with HIV-1 infection will continue to be considered as having a minor cognitive disorder even if impairments in other areas (e.g., concentration, information processing speed, executive functions) become so severe that the individual can no longer work or independently carry out activities of daily living. Furthermore, depending on the pattern of cognitive impairment, an HIV-1-infected person could possibly be diagnosed with dementia later in the course of the illness with DSM-IV criteria than with the other three criteria sets.

In view of the increasing number of different diagnostic criteria sets for HAD, it is important that clinicians and investigators fully describe the criteria used for making diagnostic decisions. Further research is needed to determine the nature of the mild, as well as severe, cognitive impairment associated with HIV-1 infection. We recommend that the American Academy of Neurology AIDS Task Force (1991) definition be followed at present, since it is well suited to a subcortical disease process, provides well-defined criteria for both the mild and the more severe disorders, and has been developed by a consensus panel of a broad group of experts in the field. It should be noted, however, that we disagree with the focus on motor symptoms in the characterization of both MCMD and HAD, since these symptoms may not occur at all in a significant number of patients; hence, we also disagree with the use of the term "complex." In fact, the AAN definition of HAD recognizes the problematic nature of this term in this context by promulgating three subtypes of HAD (behavioral, motor, and mixed behavioral-motor subtypes). Adopting narrow definitions of dementia in HAD (Becker et al. 1994), Alzheimer's disease (Berrios and Freeman 1991), and other dementing disorders limits our efforts to further define the dementia and to identify markers. Hence, we recommend that future research based on any of the sets of criteria discussed in this section should accommodate this important caveat.

In HIV infection, it is not clear what the relationships may be between MCMD (or mild neurocognitive disorder) and HAD or de-

lirium. The current literature suggests that mild HIV-1-associated cognitive impairment typically does not progress to dementia (McKegney et al. 1990; Saykin et al. 1991; Selnes et al. 1992), but additional information is needed from long-term longitudinal studies. Of note, our findings (Wilkie et al. 1998), along with those of Mayeux and colleagues (1993), suggest that minor cognitive alterations associated with early-stage HIV-1 infection are predictive of an increased risk of mortality.

Prevalence

Based on the current literature, there is no reliable estimate of the incidence of HAD, in part because a clear diagnostic guideline has not been available and because studies have differed in their operational definitions of dementia, sources of subjects, and stages of infection (Bornstein 1994). Navia and colleagues (1986b) reported that a dementia complex was observed in nearly two-thirds of their sample of AIDS patients. The estimates have been somewhat lower in recent studies, ranging from 14% per year among individuals not previously treated with zidovudine (formerly azidothymidine, or AZT), with a cumulative rate over 2 years of 28% (Day et al. 1992), to an annual rate of approximately 7% in the Multicenter AIDS Centers Study (MACS; McArthur et al. 1993) and a cumulative rate of 12.3% in Europe (Chiesi et al. 1996).

As discussed by Grant and Martin (1994), the discrepancies in the prevalence of HAD between studies may in part result from differences in the definitions adopted. Although in adults, HAD typically does not develop before constitutional symptoms, immune deficiency, and systemic opportunistic infections, the rate of a dementing illness as the initial presenting symptom of HIV infection has varied among studies, from 0.4% among otherwise asymptomatic HIV-1-infected individuals (McArthur et al. 1989) to 15% among HIV-1-infected patients (Navia and Price 1987). A variety of factors may account for this variation—for example, increased age (Chiesi et al. 1996; Eisdorfer and Wilkie 1995; McArthur et al. 1993; Wilkie et al. 1995), local prevalence of monocyte/macrophage-tropic strains, gender (Chiesi et al. 1996),

and comorbidity with substance abuse and dependence (Chiesi et al. 1996).

There is, however, considerable neuropsychological evidence that a high frequency of significant but minor cognitive dysfunction occurs during the early and late symptomatic stages of HIV-1 infection (Grant et al. 1987; Heaton et al. 1995; Holland and Tross 1985; Janssen et al. 1989; Miller et al. 1990; Navia et al. 1986b; Stern et al. 1991). Among patients in the early symptomatic stage of HIV-1 infection (the stage previously referred to as AIDS-related complex, or ARC), the reported prevalence of mild cognitive dysfunction has ranged from 15% (McArthur et al. 1989; Miller et al. 1990) to 44% (Janssen et al. 1989) and 54% (Grant et al. 1987). Among patients with AIDS, the prevalence of mild cognitive dysfunction has ranged from 31% in those with newly diagnosed AIDS (Tross et al. 1985) to more than 70% in those with established AIDS (Grant et al. 1987; Navia et al. 1986b; Tross et al. 1985). In conclusion, there is general agreement among researchers that minor as well as more severe cognitive impairment may occur during the symptomatic stages of HIV-1 infection.

At this time there is less agreement regarding whether and how frequently minor cognitive changes may occur in the asymptomatic stage of HIV-1 infection. In part because of this controversy as well as the numerous methodologic differences among studies, authors reviewing essentially the same literature frequently reach different conclusions on the presence or absence of cognitive impairment in early HIV-1 infection (e.g., Bornstein 1994; Grunseit et al. 1994; Newman et al. 1995; White et al. 1995). After reviewing 57 studies focusing on neuropsychological differences between groups of asymptomatic HIV-1-seropositive individuals and control groups of HIV-1-seronegative individuals, White and colleagues (1995) noted that 32% of the studies reported significant differences, 21% had inconclusive findings, and 47% reported no significant differences. In the 30 studies reporting neuropsychological problems, such problems were nearly three times as prevalent in the asymptomatic HIV-1-seropositive groups (median prevalence rates were 35% and 12% for the asymptomatic HIV-1-seropositive groups and HIV-1-seronegative control groups, respectively). White et al.

concluded that in some asymptomatic HIV-1-infected individuals, there is a modest increase in risk for cognitive impairment that is more likely to be detected with a relatively comprehensive cognitive test battery.

In contrast, Newman and colleagues (1995) reviewed 36 articles stemming from cross-sectional studies, with follow-up evaluations available for 9 of the samples, and concluded that there was little evidence to suggest that cognitive impairment occurs during the asymptomatic stage of HIV-1 infection. However, Newman et al. did not indicate the criteria they used to determine whether a study found significant differences between asymptomatic HIV-1-seropositive subjects and HIV-1-seronegative control subjects. Indeed, they classified the study by Wilkie and colleagues (1990) as not showing a significant difference between the HIV-1-seropositive group and the HIV-1-seronegative control group, whereas White et al. (1995) interpreted the study as showing such a difference. In that study (Wilkie et al. 1990), we observed deviations of one and two standard deviations from the norm/control group mean on four or more tests in 43% and 22% of the HIV-1-seropositive subjects, respectively, but in only 8% and none of the HIV-1-seronegative subjects. Further, statistically significant differences based on group means were found for tasks included in the domains measuring attention, verbal memory, and information processing speed. Therefore, it is not clear what criteria Newman et al. used in deciding whether a study demonstrated significant or nonsignificant findings.

Studies that used a more comprehensive cognitive test battery were significantly more likely to observe significant differences between asymptomatic HIV-1-seropositive subjects and HIV-1-seronegative control subjects than were studies reporting negative findings (Bornstein 1994; White et al. 1995). This finding appears to be associated with the variable nature and inconsistent presentation of the cognitive deficits observed during the early stages of HIV-1 infection, so that the more comprehensive neuropsychological test batteries—those that include measures of attention, information processing speed, and learning—were more sensitive to the pattern of cognitive alterations at this stage of infection

(Heaton et al. 1995). However, Velin and colleagues (1994) found that even among otherwise asymptomatic HIV-1-infected individuals, those with neuropsychological impairment were twice as likely to be unemployed, and those who did continue to work reported increased difficulty completing job-related activities independent of physical health status. Further, as mentioned earlier, minor cognitive changes during the asymptomatic stage of HIV-1 infection have been associated with significantly increased risk of mortality (Mayeux et al. 1993; Wilkie et al. 1998).

Reliable estimates of the incidence of HIV-1-associated minor cognitive changes are lacking. Indeed, it is difficult to describe the prevalence of cognitive dysfunction over the course of HIV-1 infection. Various investigators have used different operational definitions of cognitive impairment. Some investigators use the term "impairment" synonymously with "dementia," whereas others use it as an indication of cognitive change of lesser severity than that required to define dementia. In addition, studies have differed in the magnitude of deviation from the healthy or control group mean required to define "impairment," in the use of different normative groups or figures reported in the literature, and in the judgment of individual investigators in the determination of clinical abnormalities (Bornstein 1994; Grant and Martin 1994; Perry 1990). Moreover, the heterogeneity of neuropsychological test performance within CDC stages (Centers for Disease Control 1986; Centers for Disease Control and Prevention 1992) is also well known (Martin 1994). Finally, as previously noted, the size of the cognitive test battery varied, and studies using a brief cognitive battery (in some cases, taking less than 30 minutes) were less likely to detect mild cognitive impairment than were studies using longer batteries. It is not surprising, then, that estimates of the prevalence of cognitive impairment have varied widely among studies across the clinical spectrum of HIV-1 infection.

As will be discussed in more detail later, the discrepant findings on mild HIV-1-associated cognitive impairment are also, in part, the result of differences between studies in the cognitive and motor tasks used (White et al. 1995). Furthermore, in evaluating cognitive test performance, it is important to consider the degree to which

potentially confounding variables were controlled; such variables include age, education, ethnicity, primary language, alcohol use, recreational substance use, use of prescribed psychotropic medications, mood (particularly depression and anxiety), presence of Axis I psychopathology, and use of antiretroviral, immunostimulant, or other therapies for HIV-1 infection (e.g., Bornstein 1994; White et al. 1995; Wilkins et al. 1990).

Risk Factors

Although the exact frequency of HAD is unknown, it is generally accepted that a substantial number of symptomatic individuals with HIV-1 infection will experience significant cognitive loss, with the number depending in part on the stage of infection (increasing at the more advanced stages) and whether neurological complications are already present (Grant and Atkinson 1990; Perry 1990; Price et al. 1990). At this time, however, little is known about the course of cognitive changes that precede the development of HAD. Further, little information is available on the multiple mechanisms potentially underlying cognitive deficits or on the variables that might identify individuals at risk for developing HAD or MCMD. As mentioned earlier, however, some evidence suggests that increasing age is a risk factor for HIV-1-associated cognitive impairment (Chiesi et al. 1996; Eisdorfer and Wilkie 1995; Goodkin 1995; Janssen et al. 1992; McArthur et al. 1993; Weiler et al. 1988; Wilkie et al. 1995).

Among cases of AIDS reported to the Centers for Disease Control and Prevention (CDC), Janssen and colleagues (1992) reported a linear increase in the incidence of encephalopathy with increasing age (15–34 years, 6%; 35–54 years, 8%; 55–74 years, 12%; and ≥75 years, 19%). They noted that their findings best describe HAD as an initial manifestation of AIDS, since the CDC reporting system does not monitor the occurrence of additional AIDS-defining conditions after AIDS has been defined. Furthermore, their estimates probably underestimate the incidence of cognitive impairment in HIV-1-infected individuals for several reasons: 1) dementia frequently does not develop until the later stages, 2) many older indi-

viduals with dementia are never tested for HIV-1, and 3) cases of milder cognitive impairment would not meet the CDC criteria for a diagnosis of HAD.

Goodkin (1995) has concluded that MCMD and HAD will become major foci for clinical care as the incidence of HIV-1 infection continues to increase, antiretroviral drug development continues to increase the incubation period from infection to AIDS, prophylaxis of lethal complications of HIV-1 infection continues to increase survival time, and HIV-1 continues to replicate in brain, rendering cognitive syndromes relatively more prominent to patients in their quality of life and to physicians as a focus in primary care.

Preliminary findings from Wilkie and colleagues (1995) suggest that HIV-1 may have a greater adverse impact on cognitive function in older (≥50 years) than in younger (20–39 years) individuals. Older subjects with HIV-1 infection tended to have slower information processing speeds on complex decision-making tasks, more difficulty in organizing information and shifting sets, and decreased learning and greater proactive interference effects during learning than their younger HIV-1-infected counterparts and HIV-1-seronegative younger and older control subjects. It should be noted that many of the studies on the cognitive effects of HIV-1 infection (cf. Velin et al. 1994; Wilkie et al. 1990, 1992) excluded individuals in their 50s and 60s in an effort to avoid the potentially confounding effects of normal age-related changes in cognition. In view of the fact that in an estimated 15% to 20% of newly diagnosed cases of HIV-1 infection the individual is more than 50 years of age, there is a need for further research to determine whether HIV-1 infection does have a greater adverse impact on cognition in older than in younger individuals with this disease. In fact, HIV-1 infection and aging may have a truly synergistic effect on cognitive impairment, since both increase the brain's concentration of oxidative free radicals, which are toxic to neurons. There is also a need to identify the pattern of HIV-1 effects on cognition in older individuals to prevent the misdiagnosis of other dementias. This is a particularly important area, given that HAD, unlike dementias such as Alzheimer's disease, may be reversible.

Nutritional deficiencies are common in HIV-1-infected individuals (Kieburtz et al. 1991; Mantero-Atienza et al. 1991), and the effects of such deficiencies may be confused with cognitive impairment due to HIV-1 infection. In our laboratory, the speed of processing information, especially from semantic memory, was associated with vitamin B_{12} deficiency (Beach et al. 1992). In a longitudinal follow-up study of the subjects in that study, vitamin B_{12} replacement therapy was accompanied by an improvement in processing speed. In contrast, subjects who became deficient in vitamin B_{12} during the follow-up period showed a significant slowing in the speed of processing information in semantic memory (Shor-Posner et al. 1995). Vitamin B_{12} deficiency has been associated with pathological effects in the spinal cord, brain, optic nerves, and peripheral nerves, all of which can be reversed by supplementation (Kieburtz et al. 1991). Likewise, deficiencies in serum vitamin B_6 levels were accompanied by a wide variety of cognitive impairment, ranging from decreased memory to a slowing in simple reaction time (Wilkie et al. 1991). Hence, specific micronutrient deficiencies (as well as macronutrient deficiency) should be screened for in HIV-1-infected individuals with cognitive impairment.

Assessment

A constellation of cognitive, behavioral, and motor processes need to be evaluated in order to diagnose HAD as well as to identify minor cognitive disorders associated with HIV-1 infection (MCMD). As previously discussed, the cognitive effects of HIV-1 infection appear to involve the subcortical and frontocortical brain structures, and therefore the cognitive profile is different and in many cases more subtle than that in cognitive disorder associated primarily with "cortical structures," such as Alzheimer's disease. Indeed, many cognitive instruments frequently used in assessments of Alzheimer's disease are not especially sensitive to the cognitive effects of HIV-1 infection except during the late stages of dementia. An example of such an instrument is the Mini-Mental Status Exam (MMSE; Folstein et al. 1975), which is widely used in studies of

Alzheimer's disease. Only a relatively small number of asymptomatic HIV-1-infected individuals may be expected to score a few points lower on the MMSE than healthy control subjects (Wilkie et al. 1990). In contrast, a more extensive cognitive battery—one that includes complex memory, abstraction, and choice reaction time measures—yields a more detailed profile of the nature of the cognitive alterations associated with mild but significant cognitive impairment most frequently observed in HIV-1 infection (Heaton et al. 1995; White et al. 1995; Wilkie et al. 1990).

Cognitive Function

The National Institute of Mental Health (NIMH) AIDS Neuropsychology Workgroup (Butters et al. 1990) developed both a brief and a longer test battery for use in evaluating cognitive function of individuals with HIV-1 infection. Although it may not be feasible to use all of the specific cognitive measures recommended by this group, an effort should be made to include tasks within the cognitive domains specified and to include traditional neuropsychological measures as well as measures of information processing speed.

Working within the framework of the NIMH recommendations for the assessment of cognitive function in individuals with HIV-1 infection, we present some findings on specific cognitive processes that may be altered in HIV-1 infection. It should be noted that in some cases the findings are contradictory within the same stage of infection, and this emphasizes the need to consider possible confounding variables (e.g., nutrition), as will be discussed later in this section. Since HIV-1 disease is a relatively recent phenomenon, it may be helpful to integrate findings on other diseases classified as subcortical dementias—i.e., Huntington's disease, Parkinson's disease, progressive supranuclear palsy (Albert et al. 1974; Cummings 1993; Lerner and Whitehouse 1994).

Attention. Tasks that may be sensitive to alterations in attention associated with HIV-1 infection include the timed paced serial additions task (Grant et al. 1987; Heaton et al. 1995) and a reaction

time task, presented by computer, that involves a variable interval between the warning signal and stimulus (Wilkie et al. 1990). Mixed findings have been observed with the Digit Span subtest of the Wechsler Adult Intelligence Scale—Revised (WAIS-R). Tross and colleagues (1988) observed differences between AIDS patients referred for neurological evaluations and HIV-1-seronegative control subjects, and Stern and colleagues (1991) distinguished between HIV-1-seropositive subjects with mild or no symptoms and control subjects on this test. In contrast, other studies (e.g., Heaton et al. 1995; Lunn et al. 1991; Miller et al. 1990; Rottenberg et al. 1987; Saykin et al. 1988; Selnes et al. 1990; Wilkie et al. 1990, 1992) did not distinguish HIV-1-seropositive and HIV-1-seronegative groups on the basis of Digit Span subtest performance. As described below, different aspects of attention in HIV-1 infection can also be studied with other reaction time paradigms.

Speed of information processing. Performance on cognitive tasks can be examined in terms of accuracy (i.e., number of correct responses) as well as the time required to perform a task. Some tasks have been designed to disentangle the time required to mentally perform different aspects of a task from the motor time associated with pressing a key to register a response. This approach is important in studying cognitive dysfunction in HIV-1 infection because a slowing in the speed of processing information is a major characteristic of this disease (Fitzgibbon et al. 1989; Law et al. 1995; Miller and Wilkie 1994; Navia et al. 1986b; Perdices and Cooper 1989). In other diseases involving a subcortical dementia (e.g., Parkinson's disease and Huntington's disease), the slowing in information processing speed (bradyphrenia) is distinct from the retardation of movement (bradykinesia) (Cummings 1993; Lundervold et al. 1994). Although a slowing in processing speed has been observed in all stages of HIV-1 infection, it typically is a more severe problem and appears to involve more mental functions in later, rather than earlier, stages of this disease (Dunlop et al. 1992; A. Martin et al. 1992; E. M. Martin et al. 1992a, 1992b; Miller and Wilkie 1994).

Selected findings suggest that in HIV-1 infection 1) psychomotor slowing can be distinguished from an impairment in the ability to

direct attention (Law et al. 1995), 2) the detection or recognition of a signal may not be affected as much as is the time required to make decisions (Dunlop et al. 1992; A. Martin et al. 1992; E. M. Martin et al. 1992a; Wilkie et al. 1990, 1992), 3) search speeds in long-term memory (Wilkie et al. 1990, 1992) may be affected more than search speeds in immediate memory (E. M. Martin et al. 1993; Wilkie et al. 1990, 1992), and 4) slowing in processing speed appears to be independent of depressive mood changes (Mapou et al. 1993; Wilkie et al. 1990) and a history of the social use of alcohol (Rodriguez-Menendez et al. 1995).

Since reaction time measures are not subject to ceiling effects, they can be sensitive indicators of cognitive performance in the early stages of HIV-1 infection and are included in the cognitive battery recommended by the NIMH AIDS Neuropsychology Workgroup (Butters et al. 1990).

As noted earlier, we found that processing speed during certain mental operations may be associated with vitamin deficiencies, with replacement therapy being accompanied by faster processing speed (Beach et al. 1992; Shor-Posner et al. 1995; Wilkie et al. 1992). Further, A. Martin and colleagues (1992) found, in both cross-sectional and longitudinal studies at all stages of HIV-1 infection, that a slowing in reaction time was associated with higher cerebrospinal fluid (CSF) levels of quinolinic acid, which is a neurotoxin, convulsant, and *N*-methyl-D-aspartate receptor agonist. Jakobsen and colleagues (1989) observed that variability in reaction time was correlated with ventricular size in a cross-sectional study of unselected Danish AIDS patients.

Verbal memory. The memory impairment that occurs in HIV-1 infection is more similar to the "subcortical" pattern of memory impairment observed in Huntington's disease than the "cortical" pattern of memory impairment observed in Alzheimer's disease (Becker et al. 1995; Peavy et al. 1994). HIV-1-infected individuals with memory impairment would be expected to have deficits in acquisition and recall of verbal material, but these deficits are significantly diminished by recognition tests. This suggests that their impairment is primarily associated with a deficit in retrieval rather

than a deficit in the encoding and storage of information. In contrast, patients with Alzheimer's disease, a cortical type of dementia, would be expected to have deficits in recognition as well as recall, with this pattern of deficits suggesting that impairment occurs in encoding, storage, and retrieval. The California Verbal Learning Test (Delis et al. 1987) has been particularly useful in identifying patterns of learning and memory impairment associated with HIV-1 infection and can discriminate between "subcortical" and "cortical" types of learning and memory problems.

The recall of passages has been examined by means of several batteries and scales. The Wechsler Memory Scale (1945) and the Wechsler Memory Scale—Revised have been found to distinguish between HIV-1-seronegative and HIV-1-seropositive groups at different stages of infection. With a 30-minute delayed recall of the passages, Tross and colleagues (1988) observed impairment in AIDS patients referred for neurological evaluation. A longer (45-minute) delay distinguished between asymptomatic HIV-1-seropositive and HIV-1-seronegative subjects (Wilkie et al. 1990). Saykin and colleagues (1988), in a study of an HIV-1-seronegative group and an HIV-1 seropositive group with lymphadenopathy syndrome or persistent generalized lymphadenopathy (now grouped with asymptomatic subjects in 1993 CDC stage A), noted differences in immediate, but not delayed, recall of passages. In contrast, Perdices and Cooper (1990) reported that ARC and AIDS patients differed from control subjects in both immediate and delayed recall of passages. The Buschke Selective Reminding Test, which involves learning of 12 unrelated but meaningful words over six trials, has been used to assess passage recall in individuals in the early stages of HIV infection. Several studies reported significant differences in recall between asymptomatic and mildly symptomatic HIV-1-seropositive and HIV-1-seronegative groups (Stern et al. 1991; Wilkie et al. 1990).

At this time it is not known to what extent, if any, differences in methodology explain the discrepancies among the findings of different studies on recall. For example, Goethe and colleagues (1989), using the Buschke Selective Reminding Test, did not observe differences between asymptomatic HIV-1-seropositive and HIV-1-

seronegative individuals in learning and memory. However, the HIV-1-seronegative group in this study was selected to have a history of closed head trauma, and the authors' method of using the Buschke Selective Reminding Test differed from that utilized by Stern et al. (1991) and Wilkie et al. (1990). They did observe that when the HIV-1-seropositive subjects in their sample were bifurcated according to whether a CSF measure of blood-brain barrier integrity—the IgG-albumin index—was normal or abnormal, those with abnormal indices had significantly lower scores in consistent retrieval on the Buschke Selective Reminding Test.

Using the California Verbal Learning Test, Peavy and colleagues (1994) found that as a group, symptomatic HIV-1-infected individuals had significant impairment on measures of acquisition and retention and used semantic clustering strategies less often than did HIV-1-seronegative control subjects. Although the symptomatic HIV-1-infected group had impaired delayed recall, their recognition memory was normal. The asymptomatic HIV-1-infected group's performance fell in between that of the symptomatic HIV-1-infected group and the HIV-1-seronegative group on almost all measures of the California Verbal Learning Test, suggesting that a subgroup of asymptomatic individuals may have mild deficits in verbal learning and memory. The profile of learning and memory deficits observed in the symptomatic HIV-1-seropositive group was similar to that observed in patients with Huntington's disease and was distinguishable from that observed in patients with Alzheimer's disease.

Visuospatial memory. Visual memory impairments have also been noted in AIDS patients (Lunn et al. 1991; Tross et al. 1988; van Gorp et al. 1989), though variable results have been reported concerning these abilities. Several (Tross et al. 1988; Van Gorp et al. 1989), but not all (Lunn et al. 1991), studies using the Block Design subtest of the WAIS-R noted differences between subjects with AIDS or asymptomatic HIV-1-seropositive individuals and HIV-1-seronegative control subjects (Stern et al. 1991; Wilkie et al. 1990). Wilkie and colleagues (1990) found that the speed of visual search and discrimination distinguished between the asymptomatic HIV-1-seropositive group and HIV-1-seronegative control groups.

Abstraction. The frontal lobes are involved with processes that monitor, direct, and control behavior and include functions such as concept formation, abstraction, reasoning, hypothesis generation, and set shifting. As discussed by Cummings (1993), there are dense projections between the frontal cortex and the caudate nucleus, with these connections providing an anatomic basis for the similarities between subcortical dementias and frontal lobe syndromes. Nonverbal reasoning and concept formation, as measured by the Category Test (e.g., Grant et al. 1987; Heaton et al. 1995; Joffe et al. 1986) and Trail Making Test B (e.g., Heaton et al. 1995), distinguished between subjects with AIDS and HIV-1-seronegative control subjects. E. M. Martin and colleagues (1992a) found that a computer-presented version of the Stroop Color Word test was more sensitive than the traditional version of this task in distinguishing between both asymptomatic and symptomatic HIV-1-seropositive subjects and an HIV-1-seronegative control group.

Language. Performance on language tests that involve highly overlearned information tends to remain relatively stable over the course of HIV-1 infection (Grant et al. 1987; Lunn et al. 1991; Stern et al. 1991; Tross et al. 1988; van Gorp et al. 1989; Wilkie et al. 1990). Timed word list generation may be an exception (Saykin et al. 1988; Stern et al. 1991; Tross et al. 1988; van Gorp et al. 1989) but is not a consistent finding (e.g., Heaton et al. 1995). In addition, Saykin and colleagues (1988) noted differences between HIV-1-infected individuals with lymphadenopathy syndrome and control subjects on a number of language measures, including the Boston Naming Test, Controlled Oral Word Association (using the letters *F, A,* and *S*), and animal naming. These results in HIV-1 infection are supported by those in other subcortical dementias in which language processes are also generally spared. However, there is limited information available on language functions during the late symptomatic stages of HIV infection, so it is not clear that generalizations of findings from earlier stages of the disease are appropriate.

Motor processes. Motor slowing and impaired fine motor control in HIV-1-infected individuals, as measured by the timed Fin-

ger Tapping test, Grooved Pegboard test, and a dynamometer measuring hand grip strength, have been well documented (e.g., Heaton et al. 1995; Lunn et al. 1991; Rottenberg et al. 1987; Saykin et al. 1988; Tross et al. 1988). Whereas Selnes and colleagues (1990) and Miller and colleagues (1990) did not find statistically significant differences between asymptomatic and symptomatic HIV-1-seropositive and HIV-1-seronegative groups on the Grooved Pegboard test, Heaton and colleagues (1995), after controlling for depressed mood, did find such differences in motor function.

Overall mental status. A practical, gross screening examination frequently used in studies of dementia among the elderly is the MMSE (Folstein et al. 1975). A score 1 standard deviation (SD) below the mean—for example, 26 (>3 SDs below the mean for a group of HIV-1-seronegative homosexual male control subjects)—corresponds to the lowest quartile cutoff score for cognitively normal men and women in their 80s (Bleeker et al. 1988). However, this test is more sensitive to cortical than to subcortical dysfunction, and performance on this test may fall within the normal range in early HAD.

Podraza and colleagues (1994) used the Dementia Rating Scale, along with an extensive neuropsychological evaluation, to assess differences in cognition between HIV-1-infected individuals at all stages and an HIV-1-seronegative control group. The subjects were, on average, in their 30s. The investigators found slight but significant differences between the groups, with the HIV-1-infected subjects in the symptomatic stage having lower Dementia Rating Scale scores (mean ± SD = 139 ± 5.8) than their asymptomatic HIV-1-infected counterparts (141.7 ± 2.9) and the control group (142.6 ± 1.4). More recently, a rating scale specifically developed to screen for HAD was shown to discriminate patients with HAD from other HIV-1-seropositive individuals (Power et al. 1995) at a cutoff score of 10 points. The main advantages of the Dementia Rating Scale are that it is 1) HIV-1-specific, including timed items more sensitive to decrements in information processing speed than items in the MMSE; 2) relatively brief; and 3) easily administered and scored at the bedside. However, longer screening tests have

been advocated for this purpose, since the ability of this scale to identify HAD in HIV-infected patients remains to be demonstrated in a larger, carefully diagnosed population. When available, longer screening batteries that assess attention, memory, information processing speed, and psychomotor speed by means of the tests described earlier in this section are still considered optimal.

Functional Status

According to the American Academy of Neurology AIDS Task Force criteria (1991), a diagnosis of HAD requires the presence of cognitive impairment severe enough to impair the ability to work or perform normal activities of daily living. Functional ability can be assessed clinically but is often more reliably assessed with a standardized instrument developed for this purpose. At this time, there are no generally accepted scales available to assess functional decrements specific to HAD. Only limited data are currently available characterizing functional impairment in subjects with HAD or those in the earlier stages of HIV-1 infection (van Gorp et al. 1991). Yet, the importance of a thorough functional assessment in HIV-1-infected individuals cannot be overemphasized, and it will be necessary to standardize and integrate such an assessment within the diagnostic criteria for HIV-1-associated cognitive disorders so as to increase the reliability of these diagnoses across centers and evaluators.

Relatively gross, clinically rated measures—e.g., the Karnofsky Performance Scale (Karnofsky and Burchenal 1949)—have been used for some time to evaluate the functional status of patients with HIV infection. This scale varies from 0 (dead) to 40 (disabled and requiring special care) to 70 (cares for self but unable to carry on normal activity) to 100 (functionally normal). In addition, the Global Assessment of Functioning Scale (specific to dysfunction associated with mental health) and the Social and Occupational Functioning Assessment Scale, both of which are found in DSM-IV (American Psychiatric Association 1994), could be similarly employed, especially when the Structured Clinical Interview for DSM-IV (SCID) has been used to identify Axis I psychopathology

(First et al. 1995). Other general clinical rating scales may be applied as well—for example, the Quality of Life Index, which consists of five items (activity, daily living, health, support, and outlook) rated on a 3-point scale and requires about 1 minute for an evaluator to complete (Fayers and Jones 1983).

Clinically rated global functional status measures have been developed specifically for patients with HIV-1 infection. An example of such a measure is the staging system proposed by Sidtis and Price (1990), in which functioning is rated as 0 (normal), 0.5 (equivocal/subclinical), 1 (mild; ability to do all but most demanding aspects of daily living); 2 (moderate; able to perform basic self care), 3 (severe; major intellectual incapacity or motor disability), or 4 (end stage; nearly vegetative). More highly differentiated scales have also been developed for HIV-1-infected patients generally, though not for HAD patients specifically. Perhaps, the most frequently used scale in the setting of HIV-1 infection is a 30-item questionnaire derived from the Medical Outcomes Study (Wu et al. 1991, 1993), a shorter version of which has been developed (Bozzette et al. 1995). This interviewer-administered scale evaluates six dimensions of functional status related to health in HIV-1-infected individuals: physical functioning, role functioning, social functioning, mental health, health perception, and, especially important, pain. Rating in the six dimensions ranges from 0 to 100%, with higher scores reflecting higher functional status. Another example, though self-administered, is the Patient-Assessed Report of Status and Experience (HIV-PARSE), a generic health status measure developed by the University of California at San Diego and the Rand Corporation and adapted for use with patients with HIV infection (Rand Corporation 1989). This measure, which requires approximately 20 minutes to complete, assesses health care utilization, economic status, and personal characteristics, as well as health status and functional level.

Among the well-differentiated functional status measures established for use outside the setting of HIV-1 infection is the Sickness Impact Profile (Bergner et al. 1981), a well-standardized measure of dysfunction related to any type of physical illness. It generates both a Physical and a Psychosocial Dysfunction Category score as

well as an Overall Dysfunction score. The Physical Dysfunction Category score reflects changes in motor function, and the Psychosocial Dysfunction Category score reflects behavioral changes. Hence, a cutoff score of 1 SD greater than the mean on either scale could be used to document the presence of significant associated impairment in the motor and/or behavioral spheres required for subtyping a diagnosis of HAD as defined by the American Academy of Neurology (1991). One potential problem with the Sickness Impact Profile is that, as a self-report measure, it is subject to denial and distortions in self-perception. Yet, this measure has been used in studies of HIV-1-infected patients and has been found to be sensitive to cognitive function—specifically to measures of information processing and reaction time (Beason-Hazen et al. 1994; Weinstein 1990). These relations remained significant when the effect of depression was statistically controlled and were not significantly associated with CD4 cell level or presence or duration of symptoms (Beason-Hazen et al. 1994). The Sickness Impact Profile scores for patients in the asymptomatic stages of infection did not show significant variability (K. Goodkin et al., unpublished data) when compared with the dysfunction level scores documented among ambulatory, chronic low back pain patients (K. Goodkin, D. Dickson Rishel, J. Leeka, et al. 1990). Hence, the Sickness Impact Profile seems to be specific to actual decrements in activities of daily living related to illness rather than perceived decrements in such function due to psychological distress associated with being seropositive for HIV-1.

An observer rating scale of dysfunction would be useful to supplement information obtained from subjective, self-report scales like the Sickness Impact Profile. However, there is as yet no reliable, objective means to assess an HIV-1-infected individual's capacity to perform a broad array of functional activities of daily living. Objective measures available to assess functional ability in general in patients with medical illness have been used for patients with HIV-1 infection. One such measure, the Quality of Well Being Interview (Read et al. 1987), assigns experience over the prior 6 days to a branching response array with 2,200 discrete functional states along four dimensions: symptoms/problems (from 22 com-

plexes), mobility, physical activity, and social activity. It has been suggested that this interview is particularly useful in the functional evaluation of HIV-1-infected patients. A well-differentiated clinically rated scale standardized on elderly dementia patients—the Direct Assessment of Functional Status (Loewenstein et al. 1989)—may be useful in assessing relatively low levels of functional skills in HIV-1-infected patients. Assessment of a broad array of functions at different levels of complexity is important for treatment planning. Such an assessment provides important data for psychosocial interventions and remediation efforts as well as for evaluating pharmacotherapy and other treatment regimens.

Possible Confounding Factors in the Diagnosis of HIV-1-Associated Cognitive Disorders

In evaluating the effects of HIV-1 on cognition, it is important to consider the effects of other factors that can influence performance. A distinction can be made between performance and competence (Salthouse 1991). *Competence* refers to the level that the individual is capable of achieving under optimal evaluation conditions. In contrast, *performance* refers to the level at which the individual actually achieves in the testing situation. Although performance is used to infer competence, the two concepts are not identical. Therefore, scores on neuropsychological tests may not represent the true competence level if factors extraneous to ability are operating to suppress performance below that level. Further, the disparity between competence and performance could be confounded by serostatus and disease stage. In the following subsections, therefore, we address the relation between HIV-1 infection and each of several potential performance-limiting or ability-extraneous factors.

Changes in Self-Efficacy

It is common knowledge among individuals with HIV-1 infection that as the disease progresses, they are at increased risk for developing cognitive impairment. This awareness may increase their concerns about the likelihood of successfully performing a task.

Such a loss of perceived self-efficacy or lack of confidence in one's abilities may itself lower performance on cognitive tasks because a feeling of futility can decrease the amount of effort exerted in performing a task or because a fear of failure can increase the level of anxiety.

Attentional Mechanisms and Arousal Level

In the general cognitive literature there has been considerable interest in the view that attention (mental effort, capacity) is required to perform many mental operations. A distinction has frequently been made between the level of attention required by tasks. Some tasks require little, if any, attention and thus can be performed almost automatically. In contrast, tasks that require varying amounts of attention, frequently termed *effortful* tasks, require access to the controlled information processing system. Time pressure is a particularly important determinant of momentary effort. Tasks that place a heavy load on short-term memory, which has a limited capacity, impose severe time pressure and require attentional effort (Salthouse 1991). The major cognitive impairments associated with HIV-1 infection are slowing in the speed of processing information; verbal memory deficits; and difficulties in concentration. This suggests that attention—as a mental resource—may be a useful model on the basis of which to interpret HIV-1-associated cognitive disorders. Indeed, Satz and colleagues (1993) used an attention mechanisms model to interpret Satz's observation that HIV-1 infection had a significantly greater adverse impact on cognition in homosexual men with less than a high school education than in their better educated counterparts during the asymptomatic stage of infection. Hence, Satz et al. (1993) postulated that HIV-infected individuals with a diminished premorbid reserve capacity may be at greater risk of developing HIV-1-associated cognitive impairment.

Arousal level is believed to affect the mobilization of these already limited attentional resources. More attention is available when arousal is moderately high than when arousal is low. The attention directed toward a task varies according to the demands of the activities required to perform the task, which can cause corre-

sponding variations of arousal in and of themselves. Variations of arousal also affect the individual's policy of allocating attention to different activities. According to the Yerkes-Dodson Law (Yerkes and Dodson 1908), the quality of performance on any task is an inverted U-shaped function of arousal. Hence, poor performance may be associated with very low as well as very high levels of arousal.

Complex tasks appear to be very sensitive to the adverse effects of extremes in arousal level. Research involving HIV-1-seronegative individuals suggests that poor performance due to a state of high arousal may be associated with 1) narrowing of attention to the dominant and most obvious aspects of a task, 2) increased lability of attention, 3) failure to make fine discriminations between relevant and irrelevant aspects of task necessary to appropriately allocate attention, and 4) systematic changes in strategy during the performance of a task. In contrast, poor performance associated with extremely low arousal levels may be accompanied by decreased motivation and may cause both failure to adopt a set needed to perform a task and failure to evaluate one's own performance, resulting in an insufficient supply of attention directed toward a task. As the HIV infection progresses, the individual's arousal level may be further affected by changes in motivation, greater fatigue, disrupted sleep patterns, and increased use of medications that may have sedating effects.

Anxiety and Depressive Symptoms

In the general clinical literature, the concept of depression-associated cognitive impairment is well accepted and has been of assistance in identifying potentially treatable forms of dementia (Cassens et al. 1990). Complaints of anxious and depressive symptoms are frequent among HIV-1-infected individuals, especially during the later stages of infection (Atkinson et al. 1988; Goodkin 1988, 1995). Somatic or vegetative signs of major depressive disorder—decreased energy, weight loss, and insomnia—may occur as part of early HIV-1 disease progression and may adversely affect memory and concentration; moreover, the impaired memory and concentration is itself a symptom of major depressive disorder. Further,

the cognitive symptoms of major depressive disorder—helplessness, hopelessness, and low self-worth—are performance-limiting factors in cognitive assessment, as are the purely affective symptoms, which interfere with arousal and attention to task performance requirements.

The lifetime prevalence rates of anxiety and depressive disorders reported among HIV-1-seronegative at-risk individuals (homosexual/bisexual men and injecting substance users) are similar to those observed in HIV-1-seropositive individuals during the asymptomatic and early symptomatic stages of infection (Atkinson et al. 1988; Williams et al. 1991). As noted by Grant and Martin (1994), HIV-1-infected individuals originate from groups that, relative to the general population, are at higher risk for psychopathology. These conditions may be reactivated over the course of HIV-1 infection, a feature which points to the potential importance of this confound for natural history studies of cognitive disorders in HIV-1-infected individuals (Wilkins et al. 1990). Inconsistent findings have been reported, with a modest association between depressive symptoms and cognitive function observed in HIV-1-infected individuals in a few studies (e.g., Maj et al. 1994; Stern et al. 1991) but not all (Bornstein et al. 1993a; Hinklin et al. 1992; Mapou et al. 1993). Much of the available evidence suggests that cognitive deficits do occur in HIV-1-infected individuals independent of depression (Bornstein et al. 1993b; Grant et al. 1993; Heaton et al. 1995; Lunn et al. 1991).

Alcohol and Psychoactive Substance Use

Alcohol- and recreational substance use–related cognitive impairment must also be assessed in the HIV-infected population. First, in as many as 29% of cases of AIDS, injecting substance use was the primary risk factor for contracting HIV-1. Increased alcohol and substance use and recidivism after periods of abstinence have been reported as psychiatric morbidity related to the identification of HIV-1-positive serostatus, especially in the absence of appropriate HIV antibody test counseling (Goodkin 1988). An association of alcohol and substance use with clinical progression of HIV-1 infection (including HAD) has also been suggested (Chiesi et al. 1996;

Goodkin 1990), although this has not always been empirically demonstrated (Kaslow et al. 1989). Neuropsychological studies of HIV-1 infection frequently attempt to exclude individuals with a history of alcohol or substance abuse.

Studies of the effects of the occasional use of alcohol or recreational substances on cognition in HIV-1 infection have yielded mixed findings. Among medically asymptomatic HIV-1-infected individuals, however, the social use of alcohol and/or recreational substances combined with a history of head injury was associated with an increase in cognitive impairment overall and especially in the areas of attention, verbal memory, and speed of information processing (Claypoole et al. 1993). In contrast, we (Rodriguez-Menendez et al. 1995), along with others (Bornstein et al. 1993c; Heaton et al. 1995), found that although a history of alcohol use did affect cognitive performance independent of HIV-1 serostatus, such a history did not account for the differences in cognitive test performance observed between HIV-1-seropositive and HIV-1-seronegative individuals. In many cases, it is possible to rule out the possibility of substance use–related cognitive dysfunction as a confound in determining disorders attributable specifically to HIV-1 only if neuropsychiatric assessments exist that predate the infection. Corroborative evidence from significant others regarding duration and frequency of use and associated mental status changes can also be helpful in this regard.

Sensory Loss

HIV-1 infection is frequently accompanied by a variety of sensory impairments as the disease progresses, particularly pain and touch sensation in the extremities as well as visual impairment. Hence, one could hypothesize that sensory dysfunction contributes to decreased performance on cognitive tests. HIV-1 infection itself is associated with the most frequent abnormal finding on funduscopy in HIV-1-infected individuals (i.e., cotton wool spots); however, cytomegalovirus retinitis is the most common intraocular infection associated with severe visual loss in these patients (Whitcup 1996). Clearly, cognitive performance will be impaired if sensory limitations prevent relevant stimulus information from ever being registered.

Fatigue

Fatigue can be a performance-limiting factor. As HIV-1 infection progresses, there is frequently an increase in the constitutional symptom of fatigue, which has been related to increases in the secretion of tumor necrosis factor–α, interleukin-1 (IL-1), and interleukin-6 (IL-6). One approach to evaluate the effects of fatigue on performance is to examine the within-subject variability in reaction time during performance. Slower response speeds and greater variability could be utilized as an indirect measure of fatigue. Further, since some reaction time tasks require only a few minutes to administer (A. Martin 1994; A. Martin et al. 1992; Miller and Wilkie 1994; Wilkie et al. 1990), the same task could be repeated at different times during an evaluation, with the degree of slowing between tasks over time used as an index of the effects of fatigue on performance. Since there is little published information on the effects of fatigue on the neuropsychological test performance of HIV-1-seropositive individuals, this factor should be specifically controlled—for example, by the foregoing methods—and reported in future studies.

Pain

A final performance-limiting factor to be considered is pain. HIV-1 infection is a chronic, debilitating disease that can be accompanied by painful peripheral neuropathies, myopathies, and numerous painful opportunistic infections. Moderate to severe pain is frequently treated with narcotic agents that have sedating effects leading to diminished physiologic arousal, concentration, and slower response speeds as well as increased confusion and depressive symptoms and, in some cases, amnesia. Less severe pain, requiring nonnarcotic analgesics or no analgesic therapy, can nevertheless serve as a distracter so that the individual may divide his or her attention between the cognitive task being performed and thoughts of the pain. This may lead to a discrepancy between performance and competence, especially when the individual is performing more complex tasks requiring considerable attentional effort.

Control for Other Medical Conditions

CNS infection and tumor, metabolic encephalopathy, and toxicity from prescribed medications and other treatments as well as from alcohol and recreational substance use frequently result in psychiatric referral in patients infected with HIV-1. The most common Axis I psychopathological disorder (outside of HAD itself) associated with these Axis III disorders is delirium, another cognitive disorder manifesting with pervasive dysfunction. However, the clinician must recognize that HAD predisposes to delirium. Further, delirium may resolve with HAD, and both disorders may be present simultaneously (i.e., delirium and HAD) (American Psychiatric Association 1994). In addition, both delirium and dementia not infrequently result from multiple factors in this difficult-to-evaluate population.

Implications of HIV-1-Associated Cognitive Disorders for Psychoneuroimmunology

Until this point in the chapter it may not have been apparent how the foregoing work on HIV-1-associated cognitive impairment is related to psychoneuroimmunologic issues. In this section, we attempt to integrate the central effects of HIV-1 on the brain with the central mediating factors of psychoneuroimmunologic effects in HIV-1-infected individuals. As has been cited in other chapters in this volume, the limbic-hypothalamic-pituitary-adrenal (LHPA) axis is one mediating mechanism for associations between stressors and immunologic outcomes. However, even when this axis is examined in isolation from other neuroendocrine mediators, the relationships that may be observed are quite complex. For example, corticotropin-releasing hormone (CRH) is not simply a neurohormone secreted independently by the hypothalamus acting specifically on pituitary corticotrophs. As indicated by the term *limbic-hypothalamic-pituitary-adrenal* axis rather than *hypothalamic-pituitary-adrenal* axis, the brain—specifically the hippocampus—participates in the regulation of the release of CRH through

a noradrenergic inhibitory mechanism. Such control of glucocorticoid secretion is critical for survival, since severe deficiency or excess of cortisol is linked to major illness and eventual death. However, there are multiple sites for (e.g., pituitary, hypothalamus) and types of (i.e., rate-sensitive fast, intermediate, and delayed) negative feedback control. The hippocampus is the principal brain target site for steroids originating from the adrenal cortex and has the highest concentration of receptor sites for these hormones. Of relevance to psychoneuroimmunology, hippocampal cell loss has been reported with excessive glucocorticoid secretion, chronic psychosocial stressor exposure, and the normal aging process. Another potential contributing psychosocial factor to hippocampal neuronal loss is major depressive disorder with melancholia, since this condition is associated with nonsuppression on the dexamethasone suppression test and chronic hypercortisolemia.

These associations are particularly relevant for HIV-1-infected individuals. An increased frequency of major life stressors has been described previously in HIV-1-infected individuals (Goodkin 1988, 1995). In addition, the rate of HIV-1 infection among older individuals is increasing (i.e., now greater than 15% in those over 50 years of age). Moreover, the association of older age with an increased likelihood of HAD has also been reported (Chiesi et al. 1996; Eisdorfer and Wilkie 1995; Goodkin 1995; McArthur et al. 1993; Wilkie et al. 1995). Further, the lifetime prevalence of major depressive disorder is higher among HIV-1-infected individuals than in the general population (Atkinson et al. 1988; Williams et al. 1991). Hence, high life stressor burden, aging, and major depressive disorder all may contribute independently to hippocampal neuronal cell loss in this population.

Destruction of hippocampal neurons is also related to HIV-1 infection itself, because the hippocampus has a very high CD4 receptor density (Pert et al. 1988a, 1988b). Since CD4 receptor is a binding site for HIV-1, this suggests that 1) the hippocampus is highly susceptible to the virus and 2) the destructive effects of HIV-1 infection in brain may be compounded when chronic stressor exposure, aging, and/or major depressive disorder with melancholia are also present. The hippocampus is associated with

verbal memory function. Thus, these effects may provide a link among stressors, mood, and specific neuropsychological functions related to the progression of HIV-1. Likewise, another such function—attention and its maintenance (concentration)—has been shown to be decreased in early HIV-1 infection. Since the brain stem has been demonstrated to harbor HIV-1 relatively frequently, and since the brain stem reticular activating system is known to mediate arousal in humans, it might also be suggested that attention and concentration, like verbal memory, are particularly susceptible to the early effects of brain infection with HIV-1. Effects on arousal could also affect mental information processing speed, another measure related to early HIV-1-associated neuropsychological impairment. Moreover, as mentioned earlier, HIV-1-infected patients frequently have parkinsonian motor symptoms, which may be related to decreased CSF dopamine levels (Berger et al. 1994) and degeneration of the substantia nigra—part of the basal ganglia (also known to harbor a high load of HIV-1). Repeated stress or chronic glucocorticoid administration downregulates hippocampal adrenal steroid receptors but not hypothalamic or pituitary receptors, and this results in a premature termination of the neuroendocrine stressor response, disinhibition of CRH release, further hypercortisolemia, toxicity to hippocampal neurons, and cell death with further glucocorticoid receptor loss (Sapolsky et al. 1984, 1986).

While psychoneuroimmunologic research began with a predominant focus on cortisol and the LHPA axis, subsequent work focused on other neuroendocrine mediators of immune measures, such as norepinephrine, epinephrine, neuropeptide Y, β-endorphin, met-enkephalin, prolactin, growth hormone, and substance P. Nevertheless, the study of neuroendocrine-mediated psychoneuroimmunologic effects in HIV-1 infection has recently focused once again on cortisol, which is known to be associated with decreased proliferation of lymphocytes in response to in vitro stimulants. As is mentioned in the chapter on bereavement support groups in this volume (see Chapter 10), hypercortisolemia has been proposed to be of central and specific importance in the clinical progression of HIV-1 infection because of suppression of the pro-

duction of Th1 cytokines, enhancement of the production of Th2 cytokines, and induction of apoptosis (programmed cell death) and, more directly, through increased replication of HIV-1 itself (Clerici et al. 1994). Th1 cytokines (e.g., interleukin-2, interferon-γ, and interleukin-12) are soluble immune mediators secreted by a subset of CD4 lymphocytes that are known to maintain the salutary function of cytotoxic T lymphocytes (a subset of CD8 lymphocytes) against HIV-1 infected cells. This subset of cells has been associated with long-term nonprogression and survivorship (Cao et al. 1995). Th2 cytokines (e.g., interleukin-4, IL-6, and interleukin-10) are secreted by another subset of CD4 lymphocytes and are associated with abnormal and dysfunctional immunologic activation that has been linked to an increased likelihood of clinical HIV-1 disease progression. A Th1-Th2 cytokine shift has been shown to occur over the course of HIV-1 infection in some studies (Meyaard et al. 1994), though the role of this shift in progression of HIV-1 infection may be oversimplified (Graziosi et al. 1994; Maggi et al. 1994). Nevertheless, such a mechanism is further supported by a subsequent study documenting that cortisol, together with HIV-1 envelope peptides, produced in vitro a decrement in natural killer (NK) cell cytotoxicity not observed with either one alone (i.e., a synergistic effect) (Ahmad and Menezes 1995). Since NK cells represent another arm of the cellular immune system and one not as directly affected by HIV-1 infection as T cells (Cai et al. 1990), the maintenance of their function may be especially important for in vivo immunity in the late stage of HIV-1 disease, when the CD4 cell count has dropped to very low levels.

Regarding the central effects of hypercortisolemia, chronically disinhibited CRH release would be expected to be associated with a compensatory decrease in CRH receptor expression in normal brain tissue. However, factors contributing to opposing changes in CRH receptor expression may be involved. For example, there may be a a loss of CRH secreting neurons due to injury and decreased CRH synthesis over time; that is, loss of neurons and physiologic, regulatory feedback of receptor regulation could result in divergent effects. In one study, chronic psychosocial stress reduced the number of CRH binding sites in hippocampus—an effect related to

neuronal injury—but an increase in CRH receptor expression was observed in several other brain sites (i.e., frontal, cingulate, and claustrocortex) (Fuchs and Flugge 1995).

Of relevance here, decrements in CSF CRH levels and increased CRH receptor expression have been identified in another cognitive disorder, Alzheimer's disease, with potential therapeutic implications apparent for the use of CRH analogues. The genes for CRH receptor have been cloned, and future research could productively be aimed at correlating changes in CRH receptor number and affinity with different types of psychopathology. However, it should be cautioned that these relationships, taken together, might prove yet more complicated, since CRH itself has been identified to have a binding protein and two types of receptor, which might also bind other endogenous ligands. In addition, cleavage products of CRH, such as CRH 9-33, may displace endogenous CRH because of a higher affinity for its binding protein but may be without any activity at the receptor (Lightman 1995). Hence, future studies with careful neuroendocrine controls are required to examine the hypothesis that deficits in neuropsychological test performance and syndromal cognitive disorders (HIV-1-associated minor cognitive/motor disorder and HIV-1-associated dementia identified by standardized criteria) are associated with hippocampal, brain stem, and basal ganglia neuronal loss. Such studies are also needed to determine whether neuronal loss may be potentiated by chronic psychosocial stressors, older age, and syndromal depressive disorder, after control for self-efficacy, arousal level, mood level, alcohol and recreational substance use, fatigue, pain, and sensory function.

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Chapter 8

Immune Function, Brain, and HIV-1 Infection

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Brain disease in individuals testing seropositive for HIV-1 appears to evolve with time and with the progression of HIV-1 infection. Symptomatic HIV-1 infection of the brain may manifest with dementia (HIV-1-associated dementia [HAD]), HIV-1-associated minor cognitive/motor disorder (MCMD), or other neuropsychiatric and neurological disorders. HIV-1 infection of the brain may be shorter or longer in latency than infection of lymphoid tissue or cells. The fundamental question about HAD pathogenesis is whether there are differences in the way HIV-1 infects the brain and the peripheral immune system. Numerous ancillary questions can be raised. Is primary brain tissue infected in addition to the immune compartment of the central nervous system (CNS)? Does the breakdown in the blood-brain barrier (BBB) play a significant role

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in the pathogenesis of HAD? What is the role, if any, played by other mechanisms, both direct (viral strain, mutation, load) and indirect (cytokine mediation, autoimmune mechanism, interactions with neuropeptides and neurotransmitters)? What are the roles of the virus—the pathogen—and the immune system—the host response—in the onset of cognitive impairment and its progression from mild neuropsychological deficits to MCMD and, eventually, on to a clinically dementing state, HAD?

Clinical Correlations of Neuropsychological Deficits With Progression Markers of HIV-1 Infection

The clinical correlations of the HIV-1-associated neuropsychological deficits described in the previous chapter with laboratory and neuroimaging techniques have been investigated. The studies reviewed in this section involve 1) analyses of cerebrospinal fluid (CSF) (excluding cytokines, which are discussed later in this chapter), 2) electrophysiologic techniques, and 3) structural and functional neuroimaging techniques.

Cerebrospinal Fluid Analyses

Analyses of CSF are important for examining the mechanisms of HAD as well as for ruling out other complications of HIV-1 infection. CSF studies of patients with HAD show mononuclear pleocytosis (cell count: 4–51 cells/mm^3), as well as an increased protein level in two-thirds of the patients (range: 42–189 mg/dL) (Navia et al. 1986b). CSF protein levels parallel clinical course in one-quarter of HAD patients. The pleocytosis described is generally lymphocytic and has been noted in earlier stages of disease in asymptomatic individuals (Goudsmit et al. 1986). Several studies have documented the limited specificity for these findings: mononuclear pleocytosis in 41% and 18% and elevated CSF protein in 32% and 18% of neuropsychiatrically symptomatic and asymptomatic individuals, respectively (McArthur et al. 1988).

Intra-BBB anti-HIV-1 IgG synthesis is common in HIV-1-infected patients (Resnick et al. 1988) and appears to be associated with neuropsychiatric symptoms and, to a lesser extent, the severity of immunodeficiency in the peripheral blood (Singer et al. 1994b). The IgG index (used to quantify intra-BBB IgG synthesis) and IgG patterns on isoelectric focusing (used to detect oligoclonal bands) have been reported to be normal in nearly 50% of HIV-1-infected patients having HIV-1-specific antibody in their CSF (De la Monte et al. 1987; R. M. Levy et al. 1985). However, studies that used ultrasensitive immunofixation and silver stain techniques to detect IgG have shown that oligoclonal bands in the CSF of HIV-1-infected patients are abnormal (Resnick et al. 1988; Shapshak et al. 1988; Singer et al. 1994b) and that combined IgG oligoclonal band production and intra-BBB IgG synthesis are detected in more than 90% of the HIV-1 infected. Free light chains of immunoglobulins have been found in the CSF of 80% of HIV-1-infected patients, even in the absence of oligoclonal IgG bands and with normal IgG indices. More recently, this finding was replicated by Elovaara and colleagues (1991) and has been shown to be correlated with disease severity. However, the presence of such free light chains is even less specific to HIV-1-infected individuals with neurological complications than the other immunoglobulin findings (Gallo et al. 1988).

These studies suggest that a dysregulation of immunoglobulin production by intra-BBB activated B cells may characterize the pathophysiology of HAD—as a complement to what is well established with progression in the periphery. Indeed, anti–myelin basic protein IgG—a possible source of myelin damage (known to occur in HAD)—was found in the CSF early in HIV-1 infection and was particularly associated with cognitive-motor dysfunction (Maimone et al. 1994). A role for dysregulated immunoglobulin production also is supported by a study of asymptomatic, HIV-1-infected homosexual men in which subclinical neuropsychological deficits were correlated with deficits in peripheral blood lymphocyte responses to pokeweed mitogen (a T cell–dependent B cell mitogen) (Wilkie et al. 1990; F. L. Wilkie, personal communication, January 1997). Furthermore, M. Kumar and colleagues (1989) have

reported that the presence of brain-reactive antibody in serum was characteristic of HIV-1-infected patients with neuropsychological complications; however, the CSF of this group was not obtained and the applicability of these results to HAD pathophysiology is, therefore, lacking in support at this time. Furthermore, a subsequent study cast doubt on the extent to which brain-reactive antibodies might play a major role in the pathophysiology of HAD (Trujillo et al. 1994). However, other studies suggested that a role of autoantibodies—for example, anticardiolipin antibodies, part of a heterogeneous group of antiphospholipid antibodies—may yet prove prominent (Brey et al. 1991). The origin of such brain-reactive antibodies remains unknown, but they are thought to be the result of expansion of a specific B cell clone(s) that is brought about by the loss of regulatory T cells through the progression of HIV-1 infection. The hypothesis that polyclonal B cell stimulation, which can be detected in serum, may be a specific immunologic predictor of HIV-1-associated neuropsychological impairment still deserves further study.

Nonspecific markers of immunologic activation also have been investigated in the CNS. Level of β_2-microglobulin, a protein present on all nucleated cells and a marker of cell membrane turnover as well as abnormal immunologic activation, has been identified as a progression index for HIV-1 infection (de Martini and Parker 1989). Elevations of greater than 2.5 μg/L in serum and 2.2 μg/L in CSF have been shown to be relatively specific for neurological symptoms (Elovaara et al. 1989, 1993). In addition, the degree of elevation of β_2-microglobulin has been found to parallel the severity of clinically characterized immunodeficiency in asymptomatic, early symptomatic (with non–AIDS-defining symptoms), and late symptomatic (i.e., with AIDS) patients. Another study examined neopterin level, a progression index of HIV-1 infection related to macrophage activation and interferon-γ secretion, in addition to β_2-microglobulin level. Both of these markers were significantly intercorrelated in serum and CSF, though not interchangeable, and this suggests a relatively parallel development of CNS and peripheral immunodeficiency (Sonnerborg et al. 1989).

Virus can be isolated from CSF, but, again, monitoring response

to treatment has relatively little correlation with neuropsychiatric symptoms (Brew et al. 1995; Ho et al. 1985; R. M. Levy et al. 1985). In a sample of 85 adult patients with HIV-1 infection and neurological complaints, 24 were classified as having HAD and 50% tested positive for HIV-1 antigen (predominantly p24) in the CSF (Portegies et al. 1989). In another study, HAD was shown to be correlated with detectable free p24 antigen in the CSF, but there was little relationship between the severity of HAD and free p24 antigen levels (Brew et al. 1995). Although an association between HIV-1 antigen and HAD was statistically significant, this antigen was observed in only 8% of those with predominantly less severe neuropsychiatric findings (McArthur et al. 1988). Thus, p24 antigen level in the CSF does not predict neuropsychiatric dysfunction, although it does appear to reflect viral replication. It should be cautioned, however, that neither the p24 antigen level nor reverse transcriptase activity has been correlated with infective virus dose (Ho et al. 1989; Imagawa et al. 1989). Nevertheless, p24 antigen level in the CSF may yet prove useful in the diagnosis of HAD and, possibly, in monitoring response to treatment (Price et al. 1988a). This is especially true for a modification of this assay in which p24 antigen complexed with anti-p24 antibody is dissociated by an acid technique so that the total p24 binding capacity can be assessed, an approach that increases the sensitivity of the assay (Morand-Joubert et al. 1994).

Similarly, the CSF level of another component of the virus—gp120, the glycoprotein coat—is likely to be associated with the level of neuropsychological deficit and may prove to be predictive of such deficits as well, since this protein has been demonstrated to be toxic to neurons and microglial cells in culture (Buzy et al. 1992). Antibodies to the hypervariable loop (V3) of gp120 have been associated with neuropsychiatric impairment (Lucey et al. 1993). Monitoring of the level of this protein may be important for a drug in development (peptide T) that was engineered to inhibit the binding of gp120 to CD4 receptor; the pharmacokinetics of this receptor interaction have been well demonstrated (Ramsdale et al. 1993).

CSF specific monitoring in HAD is further supported by a study using the quantitative polymerase chain reaction (PCR) tech-

nique—a method for detecting proviral HIV-1 DNA—which showed that individuals with more severe neurological disease had a higher proviral load in their CSF (Schmid et al. 1994). It should be pointed out that quantitative PCR for HIV-1 ribonucleic acid (RNA) did not consistently demonstrate such a relationship (Conrad et al. 1995). Interestingly, the presence of p24 antigen in the serum and CSF has been observed to be relatively independent, and this suggests that there may be a separate axis for progression of HIV-1 infection in the CNS. Thus, it may be necessary to assess viral load directly in order to have the most sensitive measure of viral replication.

Electrophysiological Findings

Relative to CNS studies, less work has been done in correlating electrophysiological parameters with neuropsychological deficits in HIV-1 infection. Initial electroencephalography (EEG) studies in symptomatic HIV-1 infection and AIDS showed a progressive increase in the frequency of abnormalities (Gabuzda and Hirsh 1987; Gabuzda et al. 1988). Studies of asymptomatic HIV-1-infected substance abusers have shown abnormalities in EEG power spectral analyses (the fast Fourier transformation [FFT]) ranging from 25% to 40% (De Falco et al. 1989; Parisi et al. 1989). Guterman and colleagues (1988) have reported on several electrophysiological indices in a sample of asymptomatic HIV-1-infected homosexual men. In this study, 77% had abnormalities in at least one of four measures—routine EEG, FFT, visual evoked response (VER) (flash evoked), and event-related potential (P_{300}) (a positive wave 250 to 350 milliseconds after presentation of a discriminative auditory stimulus task). Increased frequencies of abnormalities in VER and the P_{300} were also found by Baldeweg and colleagues (1993).

In a more recent study, 69.7% of asymptomatic, neurologically normal HIV-1-infected individuals (vs. 6.5% of control subjects) showed one or more electrophysiological abnormalities (A. Guterman, R. E. Ramsay, M. Resillez, et al., unpublished data, 1989). Despite a low incidence of abnormalities on routine EEG (6.7%), abnormality was very frequently observed on the FFT (68.9%), as described by Parisi

and colleagues (1989). Abnormalities also were seen in 15.6% of the sample on the P_{300} and in 21.9% on the VER. Abnormalities in both measures were seen more frequently in a subsample of subjects with specific neuropsychological deficits, as described earlier.

Abnormalities in the P_{300} may be related to reduced motor speed rather than to cognition (Messenheimer et al. 1990); abnormalities in the VER may be related to demyelination, which is known to occur in HAD. Thus, in some ways, HIV-1 infection of brain may be similar to the pathophysiology of multiple sclerosis (MS) (Berger et al. 1989). MS has also been suggested to be related to human T cell lymphotropic virus infection (Koprowski et al. 1985), although this finding has not been replicated in all studies (ter Meulen 1988). HAD may also have a parallel to MS in its autoimmune aspects—for example, loss of the suppressor-inducer subset of CD4 lymphocytes (CD4+CD45RA+ cells). Electrophysiological abnormalities persisted at 6 and 12 months, with the majority of subjects having findings that either remained abnormal or progressed from normal to abnormal (A. Guterman, R. E. Ramsay, M. Resillez, et al., unpublished data, 1989). During one year, the rate of abnormality in one subsample increased from 6.7% to 20%. Future studies are needed to document longitudinal electrophysiological changes and to associate these with specific neuropsychological deficits that can be followed to clinical endpoints (i.e., MCMD and HAD).

Structural and Functional Neuroimaging Techniques

Radiologic evaluation of HIV-1-infected patients with HAD has generally not been rewarding, except when used to help exclude other neurological diseases that may complicate AIDS (Post et al. 1985, 1988, 1991). The clinical diagnosis of HAD usually antedates the radiographic diagnosis. In a retrospective clinical-radiologic-pathologic correlation study of autopsy-confirmed HAD, computed tomography (CT) and magnetic resonance imaging (MRI) were relatively insensitive in detecting the primary changes of HAD, especially early in its course (Post et al. 1988). Despite widespread lesions seen at autopsy, initial CT scan and MRI of the head usually missed or grossly underestimated primary parenchymal abnormalities associated

with HAD. CT scan and MRI of the head best detected secondary changes—that is, other CNS diseases, such as toxoplasmosis and CNS lymphoma. When primary changes associated with HAD were detected, cortical atrophy was seen in the majority of cases and demyelinating lesions were seen in the minority (typically well after neuropsychological performance deficits could be demonstrated).

As expected, MRI is significantly better than CT in detecting small, demyelinating lesions; however, high-resolution CT, with its greater spatial resolution, is preferable to MRI in differentiating a lesion from surrounding edema, discriminating between lesions in close proximity, locating lesions for biopsy, judging lesion activity, and detecting small cortical lesions with minimal edema (Grant et al. 1987; Post et al. 1985). A prospective CT/MRI study suggested that in most cases MRI is the preferable modality for clinical purposes (R. M. Levy et al. 1990), which is true regarding HAD, a demyelinating disease.

In postmortem studies of individuals with HAD, widened cortical sulci and, less frequently, enlarged ventricles were noted (Navia et al. 1986a). In fact, several studies showed a significant, positive correlation between ventricular size and reaction time and a significant, negative correlation between ventricular size and neuropsychological functioning (Jakobsen et al. 1989). MRI studies have demonstrated four patterns of abnormality: diffuse widespread involvement, patchy localized involvement, focal discrete areas of involvement, and punctate white matter hyperintensities (Olsen et al. 1988). One MRI study suggested specificity for HAD of high-signal lesions in the splenium of the corpus callosum and in the crura of the fornices (Kieburtz et al. 1990). Both sites are important for information processing: the fornix provides reciprocal innervation for the hippocampus and the mammillary bodies, while the corpus callosum provides a major interhemispheric pathway.

A prospective neuropsychological study showed that punctate white matter hyperintensities were found in a comparable number of HIV-seronegative individuals and were not associated with neurological abnormalities, CD4 cell counts, alcohol or substance use, hypertension, or smoking (McArthur et al. 1990). This suggests

that this pattern is not indicative of HIV-1 infection of the brain. However, overall, the studies conducted have not yet resolved the potential clinical impact of this MRI finding, which may be related to leukoariosis and decreased information processing speed, an early HIV-1-associated deficit. Moreover, differentiating HIV-1-associated changes from opportunistic infections in the CNS presents difficulties, especially with progressive multifocal leukoencephalopathy (PML), which, like HAD, is also associated with nonenhancing, non–mass-producing white matter disease (Singer et al. 1994a). However, one report suggests that these diseases may be differentiated by diffuse (HAD) versus somewhat discrete (PML) patterns of pallor (Balakrishnan et al. 1990).

Whereas structural imaging techniques were not found to be a sensitive indicator of early HIV-1 infection of the brain in asymptomatic HIV-seropositive individuals, functional imaging studies of HIV-1-related brain changes have yielded different results. One study using positron emission tomography (PET) to measure cerebral metabolic rate for glucose has shown two distinct patterns that are highly correlated with intersubject gray matter glucose variation and disease severity, as measured by neuropsychological test performance (Rottenberg et al. 1987). In that study, early HAD was characterized by relative subcortical (thalamus and basal ganglia) hypermetabolism, which may reflect the active infectious process. Subcortical and cortical hypometabolism accompanied later disease.

The development of radiotracers that reflect cerebral blood flow and the wider availability, compared with PET, of single-photon emission computed tomography (SPECT) imaging systems have made SPECT attractive to clinicians. SPECT provides three-dimensional information about brain perfusion and metabolism and an effective and noninvasive method for evaluating the pathophysiology of HIV-1 infection in the CNS. SPECT revealed abnormalities not seen with either CT or MRI and showed focal defects in regional cerebral blood flow that corresponded very closely to focal signs or symptoms (Pohl et al. 1988). The radiotracer ^{99m}technetium-hexamethyl propylenamine oxime (^{99m}Tc-HMPAO) has proven to be superior to ^{123}I-iodoamphetamine, since with

^{99m}Tc-HMPAO no redistribution occurs by 10 minutes postinjection and there is no intrapulmonary pooling (Miller 1990). These results have been confirmed in subsequent studies with larger samples, including one that was semiquantitative (Miller 1990). Several distinct patterns of abnormality were detected, including hypoperfusion of frontoparietal (58%), generalized diffuse (29%), basal ganglia (16%), and temporo-occipital (8%) distributions (Maini et al. 1989).

Using a different neuroimaging technique, magnetic resonance spectroscopy (MRS), Chong and colleagues (1993) showed that in their sample of 103 HIV-1-seropositive subjects, *N*-acetylaspartate (NAA):creatine ratios were decreased and were consistent with diffuse, but not focal, structural abnormalities. Increments in choline:creatine ratios were also found in subjects with abnormal structural neuroimaging findings. Another recently developed neuroimaging technique, functional MRI (fMRI), which detects blood oxygenation levels reflective of local blood flow in brain and requires only 2 seconds to collect an image, has largely replaced PET, which uses radioactive tracers and requires up to a minute to collect an image. Since fMRI can detect brain activation in response to stimuli of only 30 milliseconds' duration, it can be used for "event-related" assessment of subtle neuropsychological dysfunction in the setting of asymptomatic HIV-1-seropositive individuals who are known to manifest minimal, and even perhaps no, evidence of impairment. Cognitive improvement has been related to improvements on neuroimaging and has been reported following use of zidovudine (formerly azidothymidine, or AZT) (Pizzo et al. 1988; Schmitt et al. 1988), though this improvement may be limited to very high doses (1,000–2,000 mg/day) (Sidtis et al. 1993) that are unlikely to be well tolerated over time.

Future studies would benefit from using SPECT and MRS as adjuncts to structural neuroimaging with CT scans or MRI, respectively, as well as the technique of fMRI to enhance the early detection of HIV-1-associated deficits related to changes in regional cerebral blood flow and/or tissue metabolic abnormalities. Such studies would prove helpful in making the specific diagnosis of MCMD, in monitoring the progression of MCMD and HAD, and in evaluating response to therapy (Goodkin et al. 1997).

Neuropathology and Histopathology of HIV-1 Infection of Brain

The spectrum of clinical findings of CNS involvement in AIDS includes subtle, subclinical neuropsychiatric deficits, clinically significant neuropsychiatric deficits not severe enough to warrant a diagnosis of dementia (MCMD), and HAD (De la Monte et al. 1987; Navia et al. 1986b; Snider et al. 1983; Wilkie et al. 1990) (see Chapter 7, this volume). Neuropathological postmortem examination shows CNS involvement in AIDS in up to 80% of cases (Anders et al. 1986; R. M. Levy et al. 1985; Navia et al. 1986a; Price et al. 1986). Well-defined focal lesions found in the brain in many cases are the result of opportunistic infections (e.g., toxoplasmosis) or neoplasms (e.g., CNS lymphoma). However, an unexplained diffuse encephalopathy develops more frequently and manifests with progressive dementia as a dominant feature (Snider et al. 1983).

Central cerebral and infratentorial atrophy have been associated with memory deficits in individuals with AIDS or early, non–AIDS-defining symptomatic HIV-1 infection (Poutiainen et al. 1993). Histopathologically, the encephalopathy is associated with gross cerebral atrophy, microglial nodules, and syncytia (multinucleate giant cells). Basal ganglia are most often affected, and the hippocampus (damage to which is thought to be associated with the pathogenesis of the verbal memory impairment) also is frequently involved (Anders et al. 1986; Navia et al. 1986a; Sharer et al. 1986).

HAD in adults and children shows some brain similarities; in children, however, damage is more easily specified as secondary to HIV-1 infection alone (Belman et al. 1985; Scott et al. 1984; Sharer et al. 1986; Shaw et al. 1985). The fact that a significant proportion of pediatric AIDS is due to perinatal transmission from substance-abusing mothers may explain these differences (Curran et al. 1988).

Although these studies discounted the earlier hypothesis that HAD was the result of cytomegalovirus (CMV) encephalitis, CMV remains the most frequently described co-infection in brain at autopsy and may cause a severe dementing syndrome. The clinical presentation of this co-infection syndrome includes a CD4 cell

count of fewer than 100 cells/mm^3 and rapid progression of dementia to coma. A very high rate of coexistent CMV retinitis, as well as an increased incidence of seizures, altered sensorium, confusion, and a history of peripheral neuropathy compared with HAD, has been described (Fiala et al. 1993). In terms of pathophysiology, CMV can infect neurons or any other CNS cell type, as opposed to HIV-1. HIV-1-infected macrophages may become co-infected with CMV. Astrocytes may then be recruited to the scene, where they start increasing the production of destructive cytokines—tumor necrosis factor–α (TNF-α) (cachectin), interleukin-1 (IL-1) (the secreted β form), and interleukin-6 (IL-6)—already demonstrated to be associated with HAD. CMV seems to have a predilection for ependymal cells and infects progressively and centrifugally through the periventricular white matter. The end stage of CMV CNS co-infection with HIV-1 is a fulminant meningoencephalomyeloradiculitis. Prior to this stage, and in the context of CMV treatment in conjunction with treatment of HIV-1, this co-infection syndrome may respond differentially well to foscarnet for CMV treatment rather than ganciclovir, since foscarnet is both an antiretroviral agent and effective against CMV, as opposed to ganciclovir, which is effective against CMV only.

Detection of HIV-1 in the Brain

Most evidence indicates that HIV-1 penetrates the brain. In situ hybridization, immunocytochemistry, isolation of virus from CSF and from CNS tissue by co-cultivation with normal donor peripheral blood lymphocytes, CSF immune response, and electron microscopy have been used to detect HIV-1 in CNS tissue and in CSF. In brain, HIV-1 has been specifically detected most often in multinucleate giant cells of the monocyte/macrophage lineage, sometimes in glial and endothelial cells as well, and seldom in neurons (Cheng-Mayer and Levy 1988; Ho et al. 1985; R. M. Levy et al. 1985; Resnick et al. 1988; Shapshak et al. 1990; Sharer et al. 1986; Shaw et al. 1985; Wiley et al. 1986). Despite the infrequent findings of HIV-1 in glial cells, neurons, and endothelial cells, the presence of HIV-1 in monocyte/macrophages, multinucleate giant cells, and

microglial nodules associated with demyelination remains the primary and consistent finding in CNS tissue from individuals who died with HAD and myelopathy (Brahic and Haase 1989; Gendelman et al. 1989; Shapshak et al. 1991; Yoshioka et al. 1992). With the highly sensitive and specific PCR technique (Ou et al. 1988), HIV-1 DNA can be detected (Achim et al. 1994; Bell et al. 1993; Bockstahler et al. 1995; Boni et al. 1993; Pang et al. 1990), quantified (Fujimura and Bockstahler 1995; Pang et al. 1990), and compared in different neuroanatomic regions (Bockstahler et al. 1995; Fujimura and Bockstahler 1995). However, most investigators reported on the presence or absence of HIV-1 DNA by analyzing the frontal lobe alone and have shown HIV-1 to be found most frequently in association with areas of encephalitis (i.e., the pathologically demonstrated inflammatory process) (Bell et al. 1993; Boni et al. 1993; Pang et al. 1990). One study that compared regions of the brain showed that HIV-1 DNA is more frequently found in basal ganglia than in cortical white matter or cerebral gray matter (Achim et al. 1994).

Use of quantitative PCR to analyze HIV-1 DNA in the brain was first reported by Pang and colleagues (1990). They compared HIV-1 DNA in the frontal lobe of 18 patients and categorized the HIV-1-seropositive patients with and without encephalitis. Those with encephalitis had 30 to 400 HIV-1 copies per 10^4 cells; most of this DNA was unintegrated DNA, and those without symptoms had fewer than 15 unintegrated HIV-1 DNA copies per 10^4 cells. To compare HIV-1 DNA load quantitatively, the PCR technique needs to be carried out under conditions in which the amount amplified is proportional to the target DNA originally present in the samples and the efficiency of amplification between samples is the same (Fujimura and Bockstahler 1995). A study under these conditions (Fujimura and Bockstahler 1995) observed that the HIV-1 DNA load in the medial temporal lobe (including the hippocampus) of HIV-1-seropositive subjects was higher than that in the frontal lobe or the basal ganglia (Fujimura et al. 1997). This finding suggests a need to compare HIV-1 load also in specific neuroanatomic regions involved in cognitive and motor functions in association with HAD and not solely in a broad area of the frontal lobe or basal ganglia.

An additional application for PCR is a novel technique of in situ PCR originated by Haase and colleagues (1990) by which HIV-1 DNA inside cells can be amplified in situ for detection. Thus, the cells within which the PCR target was originally present can be identified. Using this technique, Nuovo and colleagues (1994) showed that there may be an association between HIV-1-infected neurons and astrocytes and the degree of neuropsychiatric symptoms.

Mechanisms of Penetration of the Brain by HIV-1

Direct Mechanism: CD4 Expression in Neural Cells and in the Brain

The CD4 receptor is the primary receptor for HIV-1 on lymphocytes (Hoxie et al. 1985), and it is well known that CD4-positive (CD+) cells are a reservoir for HIV-1 (Schnittman et al. 1989). CD4 has been extensively mapped in the cerebral cortex (Pert et al. 1988), and specifically on neurons and glia (Funke et al. 1987). However, studies of CD4 dependence have yielded differing results regarding infection of neural cells and CNS tissue by HIV-1. There are several reasons for these differences: the sensitivity of the procedures, the extent of CD4 expression, and the cell culture histories.

Nonetheless, these studies have provided mechanisms for HIV-1 infection in the brain. In one study, HIV-1 infection of neural cell lines was shown to be CD4-dependent (Shapshak et al. 1991), whereas in another study HIV-1 was not able to replicate in these cells (Li et al. 1990). HIV-1 has been shown to infect neural cells via a CD4-independent mechanism as well (e.g., myelin-associated glycoproteins and galactosylceramide) (Chesebro et al. 1990). This mechanism of infection has also been found for fetal neural cells (Kunsch et al. 1989), CNS (glioblastoma and medulloblastoma) cell lines (Harouse et al. 1989), and lymphoid cells (Folks et al. 1987). CD4 protein (Pert et al. 1988) and CD4 RNA were found in the brain, and both CD4 RNA and CD4 protein were detected in glial cell lines (Dewhurst et al. 1987). However, HIV-1-infected cells that

did not have CD4 or macrophage markers were detected in the CNS of children who died with AIDS (Pekovic et al. 1988). It has been shown that in brain, HIV-1-infected cells undergo a reduction in expression of these markers. This mode may be operating widely while maintaining pathogenic effects in these cells. A CD4-independent mechanism has been suggested by Poland and colleagues (1995), who showed that HIV-1 can infect primary, brain-derived human microvascular endothelial cells (associated with the BBB) in vitro.

Indirect Mechanism

The animal model provided by visna virus has resulted in many insights into the replication of HIV-1 (Haase 1986). Detailed studies have indicated an indirect mechanism by which HIV-1 could penetrate the brain—perhaps via the choroid plexus—by means of a virus-carrying "Trojan horse" (Ho et al. 1987; Peluso et al. 1985). Infected macrophages could spread virus by cell-to-cell spread, since macrophages do not produce high titers of virus (Gendelman et al. 1990; Ho et al. 1987).

Mechanisms of Latency

The life cycle of a virus such as HIV-1 comprises a complex series of steps, many of which are absolutely crucial for viral replication. Mutations involving many of these steps may result in defective virus that cannot replicate or release viable and infective progeny virus from infected cells. One such possible defect is in the integration of HIV-1 into host genomes, which is necessary for the inheritance of virus by daughter cells after cell division. Infection of human cells, such as lymphocytes, by HIV-1 generally results in the integration of HIV-1 complementary DNA (cDNA) into the host genome by a complex series of steps similar to those occurring with other retroviruses (Kulkovsky et al. 1990). Many of these steps have been confirmed in vitro (Farnet and Haseltine 1990).

It is currently thought that there is a low degree of integration (one or a few HIV-1 genomes) during cytocidal infection. How-

ever, when integration is defective and proviral (circular) cDNA copies of HIV-1 accumulate in the host cell, perturbations of HIV-1 replication result. Specifically, decreased replication has been shown to be the result of defective integration and endonuclease enzyme activities of HIV-1. Integration-defective variants are mutants unable to produce infectious virus but able to produce viral RNA and proteins (Stevenson et al. 1990). This mechanism may operate in the brain and cause pathogenic changes without cell death. As mentioned earlier, elevated levels of unintegrated HIV-1 DNA were detected in CNS tissue from patients with HAD, compared with CNS tissue from HIV-1-seropositive control subjects without dementia, and may be the result of defective HIV-1 replication (Pang et al. 1990). More study is required before the specific effects of unintegrated proviral HIV-1 DNA on CNS cell function can be determined.

Another basic mechanism of control of the replication and transcription of HIV-1 involves the long terminal repeat (LTR). Proteins produced by the virus and the host bind to the LTR and thereby control, enhance, inhibit, and modulate virus replication and gene expression. There may be different types of control in different cell types, depending on the proteins expressed within these cells. Some of the host cellular transcription factors that bind to the viral LTR and affect HIV-1 replication and transcription, such as NFκB and SP1, have been identified and characterized (Garcia et al. 1987). Gene loci of host control factors have been mapped to human chromosome 12 but have not been identified (Hart et al. 1989). A viral regulatory gene like *nef* could be involved in restriction of HIV-1 replication in the CNS. In neural cells, different degrees of regulation of HIV-1 replication were exerted by *nef* (Mellert et al. 1989). However, other studies have contradicted the putative negative regulatory role of *nef* in the replication of HIV-1 (Cheng-Mayer et al. 1989; Kim et al. 1989). A more recent study showed that the expression of *nef* in human astrocytoma cells did not influence HIV-1 LTR activity (Bachelerie et al. 1990). Therefore, additional research is necessary before these these inconsistencies can be clarified.

Other proteins that enhance HIV-1 replication include cyto-

kines such as IL-1 and TNF-α (to be discussed in detail later in this chapter). However, the relevance of these factors to CNS disease in HIV-1-seropositive individuals is not yet fully appreciated. Additional factors that influence the LTR include transactivation proteins produced by other viruses such as adenovirus, herpes simplex, and CMV (Mosca et al. 1987). However, the effects of other viruses on the regulation of HIV-1 replication in vivo have not yet been clearly established.

Proteins involved in the regulation of the cell cycle may provide an additional mechanism of influence on HIV-1 replication. The cell cycle involves the following phases: $G_{0/1}$ (resting), S (DNA synthesis), and G_2+M (cell division). An examination of this issue in lymphocytes and neurally derived cells indicated that HIV-1 production in these cells was in all likelihood independent of cell cycle (Shapshak et al. 1991).

HIV-1 Infection of the Immune System and the Immune System Response to HIV-1 in Brain

The CNS pathophysiology of HIV-1 and its relation to the immune system response in brain have begun to be explored. As previously mentioned, it has been speculated that HIV-1-infected monocytes introduce HIV-1 into brain on entry via a "Trojan horse" mechanism (Ho et al. 1987; Peluso et al. 1985). It is likely that macrophages and microglia—now thought to be the predominantly infected cell types in brain—serve principally to amplify brain infection (Price et al. 1988b). These cells may rescue latent HIV-1 and augment its production, a process that results in the acceleration of symptomatic brain disease. If lymphocytes monitor the presentation of HIV-1 antigen by macrophages, then immune progression in brain to symptomatic infection (MCMD and HAD) may be so influenced. The HIV-1-infected macrophage contributes indirectly to the pathogenesis of HAD in both its resting and its activated states. However, in the absence of any other evidence, it may also be true that macrophages directly spread HIV-1 by the inefficient cell-

to-cell mechanism described earlier, since macrophages release less virus than do lymphocytes.

HIV-1 has also been shown to infect endothelial cells, astrocytes, and oligodendrocytes (which produce myelin), although it does so less frequently than it infects macrophages and microglia (Gallo et al. 1988; J. A. Levy et al. 1986). Because of their inability to express MHC class I antigens, oligodendrocytes could escape the early cytotoxic T lymphocyte response to HIV-1 and therefore be allowed to persist until no significant host immune response could be mounted (Houff 1988). In addition to being directly affected through infection associated with viral binding to myelin-associated glycoproteins, oligodendrocytes may be indirectly affected, for example, by TNF-α, which has a cytotoxic effect on oligodendrocytes (Tyor et al. 1995) and also affects neuronal function (Soliven and Albert 1992). Alternatively, the extensive genetic changes that HIV-1 itself undergoes over time within a single host could result in adaptation to the macrophage and, as a result, productive brain infection. In addition, initial HIV-1 infection with zidovudine-resistant strains has been demonstrated and may specifically predispose to HAD, since the introduction of zidovudine (with its relatively high CSF:serum ratio of 0.6) has been documented to delay the onset of HAD.

Production of virus alone may not adequately explain the eventual development of MCMD and HAD. Early in brain infection, activated T lymphocytes produce a unique type of interferon that retards maturation of monocytes to macrophages (Narayan et al. 1982). However, local expression of MHC class II antigens is simultaneously increased, with the result that the ongoing immunologic reaction in brain is amplified (Kennedy et al. 1985). Eventually, this mechanism could result in MCMD and HAD through cumulative "bystander damage" from a limited, noncytocidal infection. ("Bystander damage" is discussed in more detail in the section on cytokines later in this chapter.)

In HIV-1 infection, a robust cellular response cannot be mounted because of immunodeficiency. In addition, the appearance of symptoms is associated with decreases in anti-p24 antibody titers and increases in p24 core antigen levels. This

suggests that a failure of local immunity in brain, together with increased numbers of infected monocytes/macrophages, rather than an aggravated immune response, causes MCMD and HAD (Rosenblum 1990). Nevertheless, each of these mechanisms may be involved, the first two in the early stages of brain infection and the last one at later stages.

As previously discussed, abnormalities in the CSF are common in HIV-1-infected individuals with and without neuropsychological symptoms. Intra-BBB IgG synthesis is the hallmark of inflammation of the CNS, and a validated formula was developed for its quantitation in units of milligrams of IgG produced per day (Tourtellotte and Ma 1978; Tourtellotte et al. 1985a, 1985b). This formula corrects for diffusion of IgG from the blood via the BBB. Elevated values of intra-BBB IgG synthesis indicate production of IgG within the CNS (Tourtellotte et al. 1985a, 1985b). As mentioned earlier, intra-BBB IgG synthesis occurs in asymptomatic HIV-1-seropositive patients and in most individuals with early symptomatic HIV-1 infection and AIDS (Resnick et al. 1988; Shapshak et al. 1988). Some leakage of IgG and albumin across the BBB occurs normally (Tourtellotte et al. 1985a, 1985b), and studies by Resnick et al. (1988) and Shapshak et al. (1988) of HIV-1-infected individuals showed that there was an absence of albumin leakage. However, with an increased frequency of opportunistic infections in the CNS late in the course of AIDS, a breakdown of the integrity of the BBB may ensue; this allows entry of lymphocyte-tropic virus from the peripheral blood into brain, which increases brain viral burden and makes it more likely that MCMD and HAD will develop. Furthermore, with the progression of HIV-1 infection, the immune response appears to lose specificity, and this results in polyclonal IgG production in both the CSF (Elovaara et al. 1988) and the blood (Schnittman et al. 1986). Decreased lymphocyte proliferative response to pokeweed mitogen and the development of brain-reactive antibodies, as previously mentioned, may contribute to another mechanism, autoimmunity, which may also lead to MCMD and HAD.

HAD has also frequently been associated with a mononuclear pleocytosis in the CSF, as previously cited, which has been shown

to be predominantly composed of CD8+ T lymphocytes, in contrast to the peripheral blood (McArthur et al. 1989). During direct infection of the CNS, soluble interleukin-2 receptor (sIL-2R) and soluble CD8 (sCD8) levels are increased in CSF, whereas in indirect, immune-mediated CNS disease associated with prior viral infection, only levels of sCD8, and not those of sIL-2R, are increased. In a study of HIV-1-infected individuals, serum levels of sIL-2R and sCD8 were higher in all of the HIV-1-seropositive individuals compared with those in the HIV-1-seronegative individuals (D. E. Griffin et al. 1990). In CSF, both sIL-2R and sCD8 increased to high levels during acute HIV-1 infection. One to 2 years after HIV-1 infection, the CSF level of sIL-2R was relatively low, whereas the level of sCD8 remained elevated, with a gradual decrease over subsequent years. Because levels of sIL-2R are elevated only in the earliest stages, this study suggests that interleukin-2 (IL-2)–driven cellular proliferation does not occur to a significant extent within the CNS. The level of sCD8 is correlated with activation of CD8+ T lymphocytes in the periphery. Its prolonged elevation is consistent with a lack of virus clearance and suggests ongoing cytotoxic T lymphocyte activity directed against HIV-1-infected CD4+ lymphocytes and macrophages, although it may also reflect attack of the immune system on normal cells (i.e., an autoimmune mechanism). Low levels of sCD8 found in patients with HAD and other neurological complications suggest that late neurological complications are not associated with increased cytotoxic T lymphocyte activity and autoimmunity in the CNS but, rather, may reflect movement toward the endpoint of the pathologic process in HAD. Soluble CD4 may also be of interest in HAD, since it may reflect neuronal and other CNS cell shedding associated with cell death and CNS pathophysiology.

Another prominent, although qualitative, feature of intra-BBB IgG synthesis mentioned earlier is the occurrence of oligoclonal bands of CSF IgG, as demonstrated by isoelectric focusing electrophoresis and immune fixation to specifically detect the IgG (Tourtellotte et al. 1985a, 1985b). Oligoclonal bands are IgG bands present in CSF and not in blood or are more concentrated in CSF than in blood when equivalent quantities of IgG are ana-

lyzed. These bands are generally cathodic, appearing at pH greater than 8. Oligoclonal bands are present in AIDS, in the early stage of symptomatic infection, and with asymptomatic HIV-1 seropositive status, thereby confirming early and continued inflammation within the brain (Resnick et al. 1988). With an affinity-mediated (Western) immunoblot procedure, restricted heterogeneity of specific antigens for individual HIV-1 proteins (p15, p17, p24, and gp41) was demonstrated in the CSF and showed a correlation with oligoclonal IgG (Dörries et al. 1989). Further support for the association of intra-BBB IgG synthesis and CSF oligoclonal bands with cognitive disorders would be provided if lesions detected by methods such as MRI and PET scans are found to correlate with intra-BBB IgG synthesis and CSF IgG oligoclonal bands in MCMD and HAD patients, as has been shown for the plaques of MS (Baumheffner et al. 1990). The correlation of oligoclonal bands, intra-BBB IgG synthesis, structural lesions, and metabolic abnormalities revealed by neuroimaging techniques, and the correlation of these factors with neuropsychological performance deficits specifically seen among HIV-1-infected individuals administered neuropsychological test batteries, clearly merit further investigation.

More questions than answers are generated by the currently available studies of the relation of neuroimmunologic measures to disease progression with regard to MCMD and HAD. A heuristic model for future investigation has been described that outlines the prevalence of HAD in relation to three stages of infection: early (latent), transitional, and late (Price et al. 1990). This model integrates *input* (latent HIV-1 in the CNS, systemic HIV-1, anti-HIV-1 immune response), *action* (HIV-1 replication, effective anti-HIV-1 responses, ineffective anti-HIV-1 responses), and *output* (virus load, immunopathology). Although such a model may be helpful in directing and fostering integration of future research findings, one of its limitations is that HIV-1 integration into the host cell genome may not be organwide and may be considerably heterogeneous by site in the brain, in which case the pathophysiology is further complicated. Hence, further efforts at model development may be necessary (Figure 8–1).

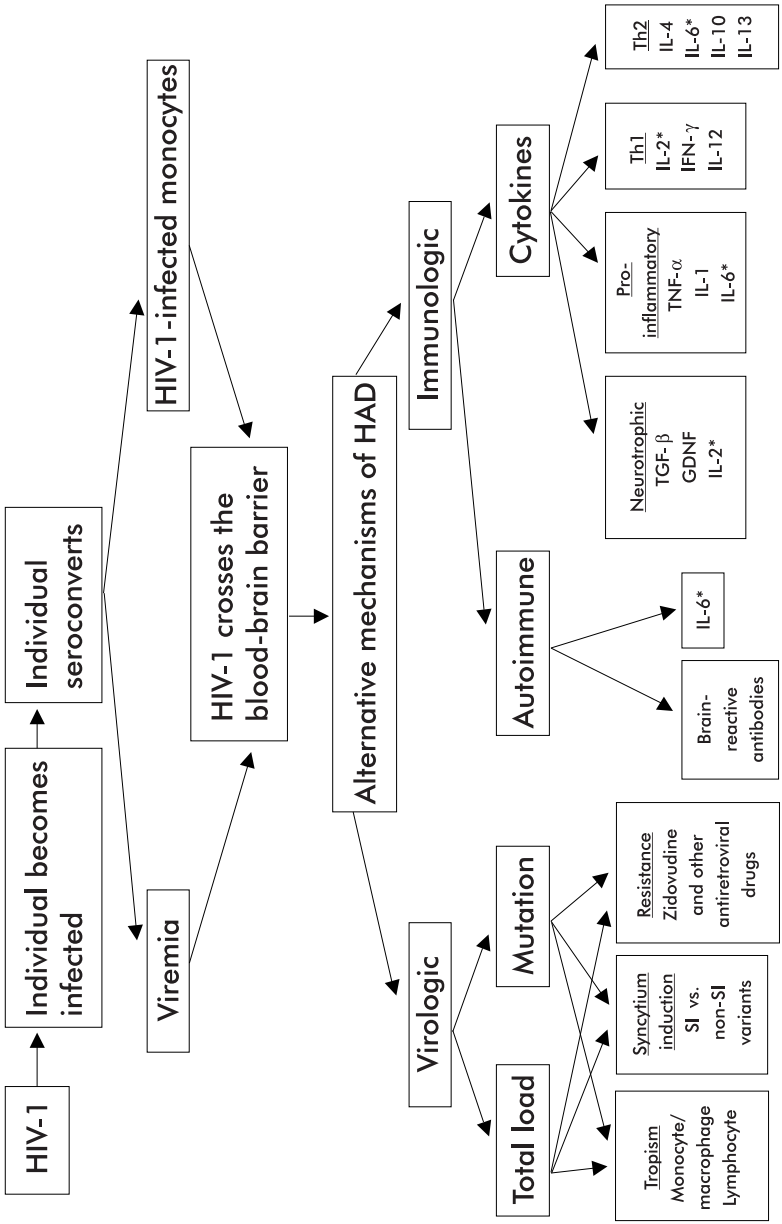
HIV-1
Individual becomes infected
Individual seroconverts
Viremia
HIV-1-infected monocytes
HIV-1 crosses the blood-brain barrier
Alternative mechanisms of HAD
Virologic
Total load
Mutation
Tropism
Monocyte/ macrophage
Lymphocyte
Syncytium induction
SI vs. non-SI variants
Resistance
Zidovudine and other antiretroviral drugs
Immunologic
Autoimmune
Brain-reactive antibodies
IL-6*
Cytokines
Neurotrophic
TGF-β
GDNF
IL-2*
Pro-inflammatory
TNF-α
IL-1
IL-6*
Th1
IL-2*
IFN-γ
IL-12
Th2
IL-4
IL-6*
IL-10
IL-13

Figure 8–1. Speculative model of the pathogenesis of HIV-1-associated dementia (HAD). HAD pathogenesis begins with HIV-1 infection of the individual, which is followed, over a variable period of time, by seroconversion. The virus may enter brain through the HIV-1-infected monocyte or, possibly, as free virus in the blood. Two main alternative axes then define the axis of intra–blood-brain barrier (BBB) progression: a purely virologic axis and an immunologic axis. The former involves increments in total viral load and strain mutation over time. The latter involves induction of autoimmunity (brain-reactive antibodies) and "bystander destruction" due to release of destructive cytokines. Progression along one or both of these axes may mediate HAD and cause changes by direct and indirect mechanisms. The viral axis is associated with direct effects associated with viral load variation across sites (e.g., frontal lobe, basal ganglia) and by specific strains (e.g., monocyte/macrophage-tropic vs. lymphocyte-tropic; syncytium-inducing [SI] vs. non-SI; drug resistance). A direct effect of immune system response includes induction of an autoimmune response and brain-reactive antibody formation. Indirect immune effects include the secretion of proinflammatory cytokines that cause bystander destruction and may feedback to the viral axis by increasing viral load (e.g., tumor necrosis factor–α [TNF-α] and interleukin-1 [IL-1]). Cytokines may be neurotrophic (e.g., glial derived neurotrophic factor [GDNF] protects dopaminergic neurons; interleukin-2 [IL-2] is associated with oligodendrocyte proliferation). In the periphery, Th1 cytokines are thought to be salutary, whereas Th2 cytokines are thought to be deleterious. However, in the CNS these roles may be reversed, with their function based on macrophage activation centrally rather than lymphocyte interactions in the periphery. For example, decrements in interferon-γ (IFN-γ), thought to be deleterious peripherally, may be salutary centrally, since IFN-γ stimulates the production of quinolinic acid, a neurotoxin associated with HAD. Similarly, decrements in interleukin-4 (IL-4) would be thought to be salutary peripherally but may be deleterious centrally because IL-4 suppresses macrophage activation. Note that IL-2, in addition to being a Th1 cytokine, is neurotrophic and that interleukin-6 (IL-6) is a proinflammatory cytokine as well as a Th2 cytokine (see asterisks). Note also that other cytokines from these groups exist but have not been selected for representation here. TGF-β = transforming growth factor–β; IL-10 = interleukin-10; IL-12 = interleukin-12; IL-13 = interleukin-13.

HIV-1 Mutants and Central Nervous System Tropism

The ability of HIV-1 to mutate extensively has been shown by analyses of restriction fragment length polymorphisms (RFLPs) on Southern blots of DNA preparations from HIV-1-infected cells (Shaw et al. 1984). There were fewer variations of specific virus isolates at different passage levels in vitro and isolates from the same individuals in vivo at successive times than there were variations of isolates from different individuals (Fisher et al. 1989; Wong-Staal et al. 1985). The individual clones derived from these isolates had extensive RFLPs (Saag et al. 1989). Thus, HIV-1 isolates are likely to be mixtures of different viral sequences and show such extensive heterogeneity that HIV-1 may be considered a rapidly evolving "quasi-species" (Goodenow et al. 1989). HIV-1 shares this and other structural properties with other lentiviruses (Narayan et al. 1982), especially visna and caprine arthritis encephalitis viruses. There may be a mechanism by which HIV-1 variants are continually generated and escape the host's immune response for a time as new variants are generated in the host (Narayan et al. 1988).

Isolates of HIV-1 from the CNS constitute a distinct group. Anand and colleagues (1989) sequenced 3,600 base pairs (bp) of HIV-1_{BR}, a strain derived from brain tissue of a seropositive individual who had progressive dementia and no opportunistic infections. The sequence of this isolate was compared with sequences of 17 other isolates of HIV-1 and was shown to be most similar to the sequence of HIV-1_{SF}, another CNS-tropic strain of HIV-1 (Cheng-Mayer and Levy 1988). Isolates of HIV-1 from the CSF and the brain have been well demonstrated to have tropisms directed more toward monocyte/macrophages than toward lymphocytes (Cheng-Mayer et al. 1989). Additional studies showed that HIV-1 isolates had differing abilities to grow slowly or rapidly and to low or high levels, respectively (Chiodi et al. 1988; Schwartz et al. 1989). HIV-1 infection of monocytes was found to lead rapidly to silent (nonproductive) chronic infection, and these monocyte-tropic variants were not cytocidal in CD4 cells (Åsjö 1989). This raises the possibility that specific molecular variants or strains of HIV-1 may be

the cause of MCMD and HAD. How may this subgroup of CNS viruses be generated? HIV-1 might penetrate the glia of brain from the migrant, latently infected macrophages, mutate during each infection cycle, and then spread to produce virus that is later isolated in the CNS and CSF.

On the basis of DNA sequencing studies and phylogenetic analysis, it has been suggested that specific strains of HIV-1 may be associated with the pathogenesis of neurological diseases in AIDS (Korber et al. 1994; Power et al. 1994). Similarities were shown between the hypervariable V3 loop of gp120 envelope glycoprotein regions of HIV-1 derived from brain biopsies and that derived from the blood of four of six HIV-1-infected patients with neurological abnormalities (Korber et al. 1994). Further, a specific amino acid signature was associated with HAD (Power et al. 1994). Using PCR, Monken and colleagues (1995) amplified a 1-kilobase (kb) region of the envelope gene (including the V1–V5 hypervariable regions) from the brain tissue of a patient and found a low level of variability in this region among the 50 cloned and sequenced products.

We analyzed sequences from the V1 through V5 hypervariable regions (including the C2 and C3 conserved regions) of the gp120 envelope gene of HIV-1 from brain, CSF, and blood from three injecting substance users. Phylogenetic analyses showed that the HIV-1 sequences separated into clusters according to their tissue or fluid source for the three patients. HIV-1 sequences from the brains of two of the patients, both of whom had CNS disease, were more similar to each other than to sequences of virus isolated from their own CSF and blood. cDNA sequences derived from HIV-1 RNA from each patient were more similar to each other than were sequences derived from proviral HIV-1 DNA from each brain tissue specimen (Shapshak et al. 1995). A subsequent study used DNA sequencing after nested PCR to amplify the V1-to-V5 region of the HIV-1 gp120 envelope gene based on brain tissue samples from as many as four neuroanatomic regions of three postmortem brains, two of which were from patients retrospectively identified with HAD. The results showed gene flow estimates indicative of independent evolution of HIV-1 populations across regions (Shapshak et al. 1999). These results suggest that regional strain variation, as

well as differences in viral load, may play a role in the pathophysiology of HAD. A T lymphocyte–tropic strain of virus became newly capable of infecting brain-derived cells after a proline in the GPGR region of the V3 loop motif of the HIV-1 envelope gene (a "hypervariable" region) mutated to serine, alanine, or threonine (Shimizu et al. 1994). In addition, tissue tropism can be selected via neutralization of antibodies against the V3 region (McKnight et al. 1995).

CNS-derived cell lines are often used as in vitro models to characterize HIV-1 replication. Srinivasan and colleagues (1988) demonstrated that transfection of an expression clone of HIV-1 resulted in HIV-1 replication in neural cell lines. Other groups reported that astrocytoma cell lines could undergo chronic infection by HIV-1 (Cheng-Mayer et al. 1987; Chiodi et al. 1987) and virus production after transfection with infectious clones of HIV-1 (Adachi et al. 1986; Dewhurst et al. 1987; J. A. Levy et al. 1986). Several groups isolated HIV-1 from CNS explants (Gartner et al. 1986; Koyanagi et al. 1987; Shapshak et al. 1992) and determined that the virus was monocyte-derived, and specifically monocyte-tropic (Gartner et al. 1986; Koyanagi et al. 1987). Christofinis and colleagues (1987) demonstrated that HIV-1 could replicate in human embryo glial cells (glial fibrillary acidic protein–positive). Shapshak and colleagues (1991) and Li and colleagues (1990) demonstrated that HIV-1 could infect and slowly replicate in neuroblastoma cells. These data show that there are biological profiles of infectivity or restriction of viruses in cell cultures. It will be important in future studies to explore the mechanisms of persistence, cytopathic effects, and pathogenesis in CNS cells.

Influence of Cytokines on the Pathophysiology of HIV-1 in Brain

During the long latency period between infection with HIV-1 and the clinical manifestations of AIDS, previously estimated to be an average of 9.8 years (Taylor et al. 1991) and lengthening, HIV-1 exists as a proviral DNA form that is integrated into the host cell ge-

nome but does not have full transcriptional activity. Before the development of AIDS, such genomic transcription is greatly activated, as demonstrated by numerous studies documenting the production of viral antigens, such as p24, in association with clinical progression (Morand-Joubert et al. 1994). Despite the more recent focus on the active dynamics of HIV-1 replication in the periphery (Ho et al. 1995), the search for factors that may drive proviral HIV-1 to become transcriptionally competent and reenter the viral replicatory cycle, as well as those factors that might deter this process, continues to be of major import in central HIV-1 infection. Many studies have suggested that cytokines may be included among these factors and may, therefore, mediate not only "bystander damage" but also direct viral destruction in the CNS. In this section, we review the cytokines that may be involved in this process and summarize the research thus far conducted on the involvement of these cytokines in the mechanisms of HAD. Cytokines thus far found to be involved in the pathogenesis of HIV-1-associated dementia (HAD) are listed in Table 8–1.

Tumor Necrosis Factor–Alpha

One of the cytokines most frequently cited regarding potential destructive effects is tumor necrosis factor–α, which is secreted by monocytes/macrophages. TNF-α has been associated with demyelination (Wilt et al. 1995), which is seen in HAD. Although TNF-α was originally cited as suppressing HIV-1 production (Wong et al. 1988), several subsequent studies have shown that it actually enhances HIV-1 replication in a chronically infected promonocyte line (Folks et al. 1987), in acutely infected monocytes (Koyanagi et al. 1988), and in a chronically infected T cell line (Clouse et al. 1989). Recombinant tumor necrosis factor alone has been shown to markedly increase the replication of HIV-1 in acutely and chronically infected T cell lines (Folks et al. 1989; Matsuyama et al. 1989). The mechanism for this effect has been described. Tumor necrosis factor–α has been shown to induce a nuclear factor, κB (NFκB). NFκB is a cytoplasmic transcriptional factor that, after activation by TNF-α, dissociates from an inhibi-

Table 8–1. Role of cytokines in the pathogenesis of HIV-1-associated dementia (HAD)

Cytokine	Role in HAD pathogenesis
Neurotrophic	
Transforming growth factor–β (TGF-β)	TGF-β constitutes a super-family of cytokines; it directly inhibits the function of IL-1 and TNF-α and may be a natural antagonist for these potentially destructive cytokines.
Glial derived neurotrophic factor (GDNF)	GDNF shows a protective effect against neurotoxins specific to dopaminergic neurons in the substantia nigra, which may be damaged or show neuronal cell loss early in HIV-1 infection of brain.
Interleukin-2 (IL-2)	IL-2, which may be related to "glial growth promoting factor," has been shown specifically to stimulate oligodendrocyte growth, potentially protecting against the demyelinating of TNF-α (see proinflammatory cytokines below) in HAD. It may have an additional role as Th1 cytokine (see Th1 cytokines below).
Proinflammatory	
Tumor necrosis factor–α (TNF-α)	TNF-α is one of the most frequently cited cytokines regarding a destructive effect. Related to demyelination seen in HAD, TNF-α is known to cause sphingomyelin hydrolysis and ceramide generation (the latter of which is an intracellular mediator of apoptosis, or "programmed cell death"). TNF-α also enhances HIV-1 replication.
Interleukin-1 (IL-1)	IL-1 stimulates HIV-1 replication. The activity of IL-1 overlaps that of "glial stimulating factor." IL-1 production is induced by "glial maturation factor," which may be an endogenous signal for reactive astrocytosis. IL-1 is cytotoxic for some cells and is known to stimulate synthesis of β-amyloid precursor proteins (β-APP).

(continued)

Table 8–1. Role of cytokines in the pathogenesis of HIV-1-associated dementia (HAD) *(continued)*

Cytokine	Role in HAD pathogenesis
Interleukin-6 (IL-6)	IL-6 is known to be involved in the normal inflammatory response to tissue damage and may be elevated as an epiphenomenon in HIV-1-associated cognitive-motor impairment in this respect (see IL-6 under Th2 cytokines below).
Th1	
Interleukin-2 (IL-2)	Also discussed above as a neurotrophic cytokine, IL-2—formerly known as T cell growth factor—is involved in the maturation of cytotoxic CD8+ T lymphocytes (CTLs) and in the augmentation of their function. CTLs are considered the major source of cellular immunologic protection against HIV-1-infected cells in the CNS.
Interferon-γ (IFN-γ)	IFN-γ enhances expression of surface MHC class II HLA-DR antigens on astrocytes; augments TNF-α and IL-1 production; stimulates macrophage neopterin secretion; causes sphingomyelin hydrolysis, inducing neuronal apoptosis; and increases the production of quinolinic acid, an excitotoxin and convulsant.
Interleukin-12 (IL-12)	IL-12 increases the production of IFN-γ and is secreted by activated macrophages, promoting an acute inflammatory response.
Th2	
Interleukin-4 (IL-4)	IL-4 is known to suppress macrophage activation; reduction in IL-4 decreases such suppression, increasing the likelihood of HAD, a disease mediated by macrophage activation.

(continued)

Table 8–1. Role of cytokines in the pathogenesis of HIV-1-associated dementia (HAD) *(continued)*

Cytokine	Role in HAD pathogenesis
Th2 *(continued)*	
Interleukin-6 (IL-6)	IL-6 may contribute to induction of an autoimmune process and brain-reactive antibody formation; however, its role in HAD pathogenesis as a proinflammatory cytokine may oppose this role (see proinflammatory cytokines above).
Interleukin-10 (IL-10)	IL-10, another inhibitor of macrophage activation, may have a similar effect as IL-4.
Interleukin-13 (IL-13)	IL-13 down-regulates the secretion of the proinflammatory cytokines TNF-α, IL-1, and IL-6, as well as nitric oxide, and shares receptor with IL-4, suggesting a salutary effect on HAD pathogenesis.

tory protein (IκB) and moves to the nucleus, where it binds to the enhancer sequence of the LTR, activating HIV-1 replication (Osborn et al. 1989). Hence, TNF-α may contribute to MCMD and HAD through demyelination and by increasing viral replication (Wilt et al. 1995) as well as decreasing neuronal function (Soliven and Albert 1992).

In addition, stimulation of HIV-1 replication by TNF-α may be inhibited by *N*-acetylcysteine, which increases intracellular glutathione and scavenges reactive, oxidative intermediates (Roederer et al. 1990). Vitamin E is also known to be an oxidative free radical scavenger and has been proven useful in the treatment of tardive dyskinesia—a syndrome associated with chronic, neuroleptic-induced dopaminergic blockade in the substantia nigra, which is affected early in CNS HIV-1 infection. Vitamin E has also been tested as a neuroprotective agent (e.g., for Parkinson's disease), and it may prove useful in high doses (3,000 IU/day or more of the *d* isomer of the α form).

Further, the lazaroids (e.g., tirilazad mesylate) are scavengers of oxidative free radicals and inhibitors of lipid peroxidation. Pretreatment with the lazaroid antioxidant drug U-74500A prevents

free radical–induced increases in calcium uptake by mitochondria (U. Kumar et al. 1994). Lazaroids (i.e., U-74389G and U-83836E) have been shown to enhance the survival of tyrosine hydroxylase–immunoreactive dopaminergic neurons, an effect which suggests that oxidative stress plays an important role in the death of cultured embryonic dopaminergic neurons and that the lazaroids may be potent neuroprotective agents in conditions in which dopaminergic neurons degenerate (Frodl et al. 1994), as occurs in HAD. U-78518F, a 21-aminosteroid from this family of compounds, increased survival of dopaminergic neurons in mesencephalic cell cultures incubated with the neurotoxin 1-methyl-4-phenylpyridinium (MPP+); protection against dopaminergic neuronal death occurred with increasing concentrations. This protective effect against MPP+-induced neurotoxicity is, in part, a function of interaction with the dopamine transporter (Sanchez-Ramos et al. 1992).

In summary, *N*-acetylcysteine, vitamin E, and the lazaroids warrant consideration as future therapeutic agents for the treatment of MCMD and HAD.

Several caveats must be cited regarding the potential contribution of TNF-α to the development of MCMD and HAD. First, HIV-1-infected monocytic cell lines do not constitutively produce TNF-α (Molina et al. 1990). Second, HIV-1 does not induce TNF-α production in the absence of endotoxin, which can be expected to be absent frequently in HIV-1-infected patients. Third, although levels of TNF-α has been found to be elevated in AIDS (Lahdevirta et al. 1988), conflicting results have been reported regarding CSF levels of TNF-α, with most studies not reporting detectable levels (Klimas et al. 1989; Tyor et al. 1995). Nevertheless, TNF-α may still exhibit local effects on HIV-1 replication in brain tissue in an autocrine fashion, and this may promote HIV-1 replication within microglial nodules without raising levels in the CSF. Should TNF-α prove a meaningful target therapeutically, several options are presently available. TNF-α blockers such as pentoxifylline, thalidomide, soluble tumor necrosis factor type I receptor, and monoclonal antibody to tumor necrosis factor could be employed. Pentoxifylline decreases whole blood viscosity and has demonstrated efficacy in vascular (multi-infarct) dementia at a dosage of

400 mg po tid (Black et al. 1992); it inhibits production of TNF-α. Thalidomide suppresses expression of TNF-α and has proven successful in the treatment of oral aphthous ulcers and wasting syndrome in HIV infection at 300 mg/day; sedation is a side effect. It is well known that thalidomide can induce severe congenital abnormalities; it may also increase Th2 cytokine secretion associated with disease progression in the peripheral blood. Hence, the potential therapeutic use of these drugs must be approached with caution, particularly with thalidomide's recent approval by the FDA for the treatment of erythema nodosum (Annas and Elias 1999).

Interleukin-1

Interleukin-1, like TNF-α, has been shown to stimulate HIV-1 replication through activation of the NFκB motif binding to the HIV-1 LTR (Osborn et al. 1989). Since both TNF-α and IL-1 are released by macrophages, TNF-α may act both in a paracrine and an autocrine fashion to increase HIV-1 replication. That is, TNF-α and IL-1 can each induce expression of the other, with the result that a positive feedback loop is established (Merrill et al. 1989). On the other hand, IL-1 may have effects on HIV-1 replication independent of TNF-α, since IL-1, unlike TNF-α, is produced by a variety of cells not belonging to the macrophage lineage, such as endothelial cells, B lymphocytes, fibroblasts, and astrocytes. Astrocytes are known to be infected by HIV-1 and demonstrate a proliferative response to "glial stimulating factor," part of the activity of which coincides with that of IL-1 (Merrill 1987). In addition, "glial maturation factor"—a competence factor for cell progression through the growth cycle specific for astrocytes—induces IL-1 production and may be an endogenous signal for reactive astrocytosis and an autocrine response that thereby enhances HIV-1 replication.

Gliosis is relevant in that it has been described as a pathologic feature of HAD (Navia et al. 1986a). IL-1 is cytotoxic for some cells either in its membrane-bound (α) or in its secreted (β) form (Inamura et al. 1989; Lachman et al. 1986) and, therefore, could play a role in cytokine induction of MCMD and HAD. IL-1 is also known to stimulate the synthesis and processing of β-amyloid pre-

cursor proteins (β-APP) in vitro. Neurotoxic effects due to chronic overexpression of IL-1α and/or the β isoform of S100—a small (10 kDa), soluble calcium-binding protein that is synthesized and released by astroglia (Van Eldik and Zimmer 1987)—have been proposed to explain progressive neurological degeneration in Alzheimer's disease (W. S. T. Griffin et al. 1989). The S100β homodimer is known to increase intraneuronal free calcium levels (Barger et al. 1992). Elevated intraneuronal free calcium levels, in turn, have been implicated in the pathogenesis of neuronal cell loss and dementia in both Alzheimer's disease (W. S. T. Griffin and Stanley 1993) and HAD (Dreyer et al. 1990); this suggests the use of the calcium channel blockers—especially those associated with N-methyl-D-aspartate (NMDA) receptors (e.g., nimodipine) (Navia et al. 1998)—as a treatment.

Of interest, the increased expression of IL-1α, S100β, and β-APP antigens has been demonstrated in brains of HIV-seropositive individuals; this suggests that IL-1α and S100β may be involved in the pathogenesis of AIDS by inducing growth of dystrophic neurites and calcium-mediated neuronal cell loss in AIDS (Stanley et al. 1994). In addition, and of relevance to psychoneuroimmunology (to be discussed in detail later in this chapter), IL-1 increases CRH release and consequent serum cortisol levels (Kavelaars et al. 1989) and decreases natural killer (NK) cell cytotoxicity as well as T cell proliferative responses (Weiss et al. 1989), all of which may have secondary effects on HIV-1 replication (see Chapter 7, this volume). As pointed out in Chapter 7, chronic stressors have been associated with hippocampal neuronal loss; such loss results in disinhibition of the limbic-hypothalamic-pituitary-adrenal axis and further hypercortisolemia (Sapolsky et al. 1986), which may add a physiological component to the negative psychological impact of psychosocial stressors. IL-1 blockers (e.g., IL-1 receptor antagonist; soluble IL-1 type I receptor antagonist) may be useful treatments for IL-1-mediated diseases (Dinarello et al. 1995) and thus, perhaps, for MCMD and HAD. The anticancer drug suramin is a reverse transcriptase inhibitor and inhibits binding of IL-1 to its receptor (Strassman et al. 1994). However, suramin does not penetrate the CNS well, and in one trial it did not generate a positive re-

sult peripherally (Cheson et al. 1987). Hence, suramin analogues with better CNS penetration, currently in development, may be required for there to be a useful therapeutic candidate in HAD.

As pointed out earlier, studies on TNF-α and IL-1 do not always support the hypothesis of the destructive effects of cytokines. One study found that mean levels of TNF-α and IL-1β produced by macrophages were reduced in AIDS compared with earlier stages of HIV-1 infection (Cox et al. 1990). At first, these results appear to be directly contradictory to those predicted by the cytokine hypothesis. However, if depressed cytokine responses are attributable to immunosuppression by HIV-1, then these results may be interpreted as consistent with the process of infection. Unlike HIV-1 infection, visna virus infection is accompanied by a prominent inflammatory response in brain (Rosenblum 1990). In HIV-1 infection, this inflammatory response may occur in the early phases, when immunocompetence is preserved, in which case the cytokines will have potentially destructive effects during this period. However, with progression of HIV-1 infection, BBB defects may occur, the CNS viral load is increased by exposure to the blood. Immunocompetence would be further compromised, and this would result in destructive effects in brain. These effects may be the result of decrements in cytotoxic T lymphocyte activity against HIV-1-infected cells (Orentas et al. 1990), though these cytotoxic T lymphocytes may also contribute to peripheral progression by depletion of antigen presenting cells (Haynes et al. 1996) and to CNS pathophysiology through the release of destructive cytokines (TNF-α and interferon-γ) in the CNS.

Interleukin-6

Another cytokine of recent interest in relation to HAD is interleukin-6. IL-6 (originally called B cell stimulatory factor) plays an essential role in the differentiation of activated B cells into immunoglobulin-secreting plasma cells. It is well known that HIV-1 infection is associated with polyclonal B cell stimulation and is associated with related diseases, such as multiple myeloma. In HIV-1-infected individuals, elevated levels of IL-6 and its mRNA

have been found (Breen et al. 1990). Recently, IL-6 and IL-1β have been found in association with HIV-1 infection, with and without HAD (Gallo et al. 1990). IL-6 in the CSF may contribute to production of anti-HIV-1 antibodies as well as to intra-BBB polyclonal IgG synthesis. Further, IL-6 has co-stimulatory effects on T cell proliferation and has been correlated with the presence of sIL-2R; this suggests that IL-6 may induce intracerebral activation of a T cell subset invading the CNS. Although the cellular source of IL-6, like that of IL-1β, is unknown in brain, it is unlikely to be derived from T cells and more likely to be derived from brain macrophages and astrocytes (Frei et al. 1989) as well as endothelial cells.

IL-6 has also been associated with specific complications of HIV-1 such as Kaposi's sarcoma (Miles et al. 1990). Whereas IL-6 has not been associated with increases in the viral load of HIV-1, it has been associated with the increase in abnormal immunologic activation of B lymphocytes associated with disease progression (Marfaing-Koka et al. 1996) and, potentially, with MCMD and HAD as well. Hence, anti-IL-6 therapies (e.g., monoclonal antibody to IL-6) may contribute to the control of MCMD and HAD. Further research on the relationship of IL-6, IL-1, and TNF-α will help in disentangling the complex set of results thus far observed among these proinflammatory cytokines.

Interferon-Gamma

Interferon-γ, like TNF-α, IL-1, and IL6, has been shown to be related to brain-immune interactions. Astrocytes activated with interferon-γ enhance their expression of surface MHC class II HLA-DR antigens (Merrill 1987). These astrocytes may present myelin basic protein to encephalitogenic T cell lines, perpetuating a pathophysiologic process culminating in HAD. In addition, interferon-γ has been shown to augment TNF-α and IL-1 production (Wright et al. 1988), and this augmented activity would be expected to lead to further enhancement of HIV-1 replication. Yet, interferon-γ has been shown to have a suppressive effect on HIV-1 replication in an acutely infected monocytic cell line and is now accepted as one of the Th1 cytokines, which have salutary effects in

terms of maintaining cytotoxic T lymphocyte activity in the periphery. Nevertheless, interferon-γ–associated macrophage stimulation results in the secretion of neopterin, which has been associated with the progression of CNS HIV-1 infection, as mentioned earlier in this chapter.

Like TNF-α, interferon-γ causes sphingomyelin hydrolysis and ceramide generation, which induces neuronal apoptosis—an indirect mechanism of cell death known to occur in HAD (Petito and Roberts 1995). It has also been shown that macrophages stimulated with interferon-γ in vitro produce large amounts of quinolinic acid (Heyes et al. 1992). Quinolinic acid is active at excitatory amino acid (NMDA [*N*-methyl-D-aspartate]) receptors and is a convulsant; of note here, approximately 25% of HAD patients have associated seizures. Increased concentrations of quinolinic acid in the CSF are correlated both with the severity of neurological impairments and with markers of immune activation both in HIV-1-infected patients and in simian immunodeficiency virus–infected macaques. The highest CSF and brain quinolinic acid levels occur in conditions of macrophage infiltration and gliosis within the CNS (Heyes et al. 1992; Martin et al. 1992). Furthermore, quinolinic acid level was found to be increased in brain tissue, especially in the basal ganglia of HIV-1-infected patients (Achim et al. 1993). Because the basal ganglia are a region rich in NMDA receptors (which mediate the neuropsychiatric effects of quinolinic acid [Cotman and Monaghan 1986]), and because inflammatory neuropathologic lesions in these areas are characteristic of HIV-1 encephalitis, quinolinic acid may act as a pathologic agonist at the NMDA receptor to mediate CNS damage in these regions.

Interferon-γ stimulates MHC class I and class II antigen expression, and both antigens have been shown to be increased in the CNS of HIV-1-seropositive individuals (Tyor et al. 1992, 1993). The presence of HIV-1 antigen in class II+ and class I+ macrophages and microglia could enable them to present HIV-1 proteins to CD4+ and CD8+ T cells, respectively. This may provide a perpetual stimulus for local amplification of the immune response. Hence, interferon-γ, though a Th1 cytokine, may have a deleterious effect in the CNS. This cytokine, through its association with

of quinolinic acid, also relates to the possible therapeutic use of NMDA receptor antagonists such as dextromethorphan (at a high dose) and memantine.

The specific effects of interferon-γ on HIV-1-associated pathology remain to be worked out in future studies concomitantly examining the effects of other cytokines. Of note, IL-12, a more recently discovered Th1 cytokine, is known to restore HIV-1-specific lymphocyte proliferative responses (Clerici et al. 1993); however, regarding the CNS, this cytokine also increases the production of interferon-γ. In addition, IL-12 itself is secreted by activated macrophages and promotes acute inflammatory response (as do TNF-α, IL-1, and IL-6). Hence, IL-12, like interferon-γ, may be a Th1 cytokine with deleterious CNS effects in HIV-1 infection.

Interferon-Alpha

Another type of interferon—interferon-α—may also cause specific CNS neuronal damage related to HAD (Rho et al. 1996). Neuronal susceptibility may be exhibited by dopaminergic neurons in the substantia nigra. Early cognitive and motor symptoms associated with HIV-1 infection include parkinsonian symptoms of bradyphrenia and bradykinesia as well as postural instability, gait abnormalities, masked facies, and slowed saccadic eye movements. In addition, lowered dopamine level has been demonstrated in the CSF of patients with HIV-related neurological disease (Berger et al. 1994).

Although interferon-α is used therapeutically in HIV-1 infection, decreases in mental information processing speed, verbal memory, and executive functions have been reported at therapeutic doses (Pavol et al. 1995). Regarding the effects on brain, then, it should be noted that chronic intracerebroventricular administration of interferon-α was found to be associated with parkinsonian symptoms in rats (Saphier et al. 1994), and this association has been related to changes in neuronal structure. Moreover, endogenous interferon-α has been related to an increased likelihood of HIV-1 disease progression in the periphery. Although the specific effects of interferon-α on HIV-1-associated CNS pathology remain to be

elucidated, potential therapeutic value may be suggested currently for naltrexone, an inhibitor of interferon-α.

Glial Derived Neurotrophic Factor

Although most cytokines are associated with destructive effects, studies with glial derived neurotrophic factor (GDNF) indicated a protective effect specific to dopaminergic neurons. This may be relevant to the destructive effects anticipated in dopaminergic neurons due to interferon-α secretion. GDNF is a member of the transforming growth factor-β (TGF-β) superfamily; TGF-β directly inhibits the function of IL-1 and TNF-α and may represent a natural cytokine antagonist of these potentially destructive cytokines in the CNS (Merrill 1992). GDNF confers protection against MPTP-induced substantia nigra toxicity, an animal model for Parkinson's disease (Tomac et al. 1995). Hence, it might be speculated that a dynamic equilibrium exists between two cytokines—interferon-α and GDNF—at the dopaminergic neuronal level in the substantia nigra and that this equilibrium determines the local structural response to challenge by whole virions and/or HIV-1 virus products such as gp120. This equilibrium may be further influenced by use of substances with abuse potential such as cocaine, which is known to cause inhibition of dopaminergic reuptake, resulting in a euphoric experience associated with dopaminergic stimulation of the ventral tegmental area of the midbrain as well as of the nucleus accumbens and frontal cortex. Cocaine withdrawal may result in the opposite manifestation—anhedonia, which is related to decreased dopamine availability (or "reserve"), and, putatively, a susceptibility to an equilibrium shift toward dopaminergic neuronal dysfunction in response to HIV-1.

Interleukin-2

Interleukin-2, formerly known as T cell growth factor, may also play a protective role in CNS HIV-1 infection. Glial growth promoting factor stimulates the growth of oligodendrocytes specifically (Merrill 1987), and IL-2 may be related to this factor. IL-2 has

been shown to induce a three- to fourfold increase in the proliferation of rat oligodendrocytes. A clear increase in myelin basic protein (MBP) mRNA occurred after IL-2 induction (Merrill 1987). Further studies are needed to determine whether IL-2 induces the MBP gene by up-regulating its transcription or translation. However, the functional integrity of myelin produced from proliferating mature oligodendrocytes remains to be demonstrated.

Other Cytokines Relevant to HAD Pathogenesis

Interestingly, two other cytokines that may prove relevant to the prevention of HAD are associated with increased peripheral progression of disease: the Th2 cytokines interleukin-4 (IL-4) and interleukin-10 (IL-10). A reduction in IL-4 mRNA has been found in the brains of patients with HAD (Wesselingh et al. 1993b). IL-4 is known to suppress macrophage activation; hence, a reduction in IL-4 would be expected to increase the likelihood of HAD, since macrophage suppression would be expected to be salutary in HAD—a disease mediated by macrophage activation. Since peripheral progression may be more closely related to lymphocytic expression of cytokines, the fact that a reduction in this Th2 cytokine results in a salutary peripheral effect may, in fact, not be contradictory but rather a reflection of specific CNS pathophysiologic mechanisms. Likewise, it might be speculated that IL-10, another inhibitor of macrophage activation, would have a salutary effect in HAD, especially since a decrease in IL-10 mRNA has been described in HIV-associated vacuolar myelopathy (Wesselingh et al. 1993a). Since interleukin-13 (IL-13) down-regulates the secretion of the proinflammatory cytokines TNF-α, IL-1, and IL-6 as well as nitric oxide, and since it shares receptor with IL-4, IL-13 may also show a salutary effect in brain. Putatively, intrathecal delivery of these cytokines could have a therapeutic effect.

Along a different line, a great deal of interest has more recently been focused on soluble factors (e.g., interleukin-16) secreted by cytotoxic T lymphocytes (a subset of CD8+ T lymphocytes) that are known to inhibit the replication of HIV-1 (Haynes et al. 1996). Low

levels of these factors in rapid peripheral progressors may result in deleterious effects centrally as well—for example, in the CSF, where CD8+ T lymphocytes predominate over CD4+ T lymphocytes.

Neurotransmitter and Neuropeptide Changes Associated With HIV-1 Pathophysiology in Brain

Several neurotransmitter and neuropeptide changes have been associated with HIV-1 infection in brain. These include changes of possible pathophysiologic importance in the systems involving dopamine, serotonin, and, possibly, acetylcholine. Changes related to CRH, glucocorticoid receptors, vasoactive intestinal peptide (VIP), and neuroleukin may also be of importance. These potential mechanisms are reviewed briefly here, since they may have specific relevance to the interaction of neuroimmunologic effects of HIV-1 in the brain with psychosocial factors.

Dopamine

As mentioned earlier, dopaminergic function is expected to play a role in a subcortical dementia involving basal ganglia, such as HAD. In fact, parkinsonian symptoms have been defined in patients with early neurological symptoms (Berger et al. 1994) through late HAD (Navia et al. 1986b). Preliminary studies have shown large decrements in CSF dopamine levels in patients with HAD and other neurologic complications (Berger et al. 1994). One hypothesis for this effect may be related to neuronal damage caused by HIV-1 in the basal ganglia, as suggested by PET studies (Rottenberg et al. 1987). Another possibility is that a subgroup of brain-reactive antibodies may react with dopaminergic neurons in an autoimmune mechanism of neuronal destruction. These preliminary findings regarding dopamine must be confirmed by future studies focusing on earlier stages of the infection.

Psychostimulants stimulate dopaminergic transmission and have been advocated for the treatment of HIV-1-associated cogni-

tive impairment. Fernandez and colleagues (1988) reported a study of psychostimulant treatment of cognitive impairment associated with early symptomatic HIV-1 infection in which methylphenidate was used on a tid dosing schedule (mean total dose = 45 mg/day), with crossover to dextroamphetamine on a bid schedule (mean total dose = 30 mg/day) if there was no response to the methylphenidate. Pharmacotherapy with either stimulant was successful in 91% of patients. Dopamine agonists other than psychostimulants may be helpful as well. L-Dopa improves motor and, to some extent, cognitive function, but its use is limited by side effects. Direct dopamine agonists (bromocriptine 15–30 mg/day; pergolide 1.5–3 mg/day) may also be viable therapeutic candidates (Kieburtz et al. 1991a). Also, indirect stimulation of dopaminergic transmission (e.g., by L-deprenyl, an MAO-B inhibitor, 10 mg/day, or by amantadine 200–300 mg/day) may also prove useful.

Serotonin

Serotonin function also has been shown to decrease in HAD as measured by decreases in CSF serotonin and its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA); these changes may even prove to be greater than those seen with dopamine (Britton et al. 1989). Interestingly, levels of quinolinic acid—an abnormal byproduct of L-tryptophan catabolism through the kynurenine pathway—and L-kynurenine have been shown to be increased in the serum and CSF of patients with HAD (Heyes et al. 1991, 1992). Quinolinic acid level is elevated after acute infection in asymptomatic simian immunodeficiency virus–infected macaques and increases over time with the development of neurological disease (Heyes et al. 1990). Levels of L-kynurenine and quinolinic acid are closely associated with levels of neopterin and β_2-microglobulin in both CSF and plasma (Heyes et al. 1992). Furthermore, CSF levels of quinolinic acid have been shown to increase over a 6-month interval, correlating with slowed reaction time, among HIV-1-infected humans who were otherwise entirely asymptomatic (A. Martin et al. 1990). Pyridoxal phosphate (the activated form of vitamin B_6) is required for decarboxylation of amino acids, for

example, in the conversion of 5-hydroxytryptophan to 5-hydroxytryptamine (serotonin). Hence, deficiency of this vitamin may likewise play a role in the development of HAD (Goodkin 1995a) (see Chapter 7, this volume).

Preliminary results show increases in CSF levels of 5-HIAA after treatment with zidovudine (Singer et al. 1990) that may correlate with the improvement in HAD noted after treatment with zidovudine. This suggests that a group of drugs normally used in the treatment of major depressive disorder and obsessive-compulsive disorder—the selective serotonin reuptake inhibitors (SSRIs)—may also play a role in the treatment of HAD. For example, fluoxetine, sertraline, paroxetine, or fluvoxamine may be considered. However, the SSRIs are associated with a toxic "serotonin syndrome," as well as orgasmic dysfunction and other sexual function side effects reported in as many as one-third of patients. At present, the most important role for these agents is in the treatment of the behavioral and the mixed behavioral/motor subtypes of HAD (American Academy of Neurology 1991) as well as HAD in patients with a history of or concurrent major depressive disorder.

Acetylcholine

Acetylcholine, like dopamine and serotonin, also has been implicated in the pathogenesis of HAD. Choline acetyltransferase activity—of major significance in Alzheimer's disease—has been shown to be reduced in the frontal lobe and hippocampus of AIDS patients, with the greatest reductions in patients with severe HAD (Navia et al. 1986c). Cortical hypometabolism seen in late HAD is consistent with altered subcortical projections noted in earlier stages of the disease (Rottenberg et al. 1987). In general, the acetylcholinesterase inhibitors could prove efficacious in HAD; for example, physostigmine at low doses enhances memory but has a short half-life. Tacrine hydrochloride (Cognex)—which has been approved by the FDA for treatment of cognitive impairment—is a longer-half-life drug that may prove useful (Weiner et al. 1991); donepezil (Aricept) may prove useful as well. Acetyl-L-carnitine occurs naturally and may increase the formation of acetyl co-

enzyme A and acetylcholine; it has minimal side effects at a dosage of 1 g/day. Potassium channel blockers may play a role in the future; nonselective blockers can potentiate acetylcholine release. Linopirdine stimulates the release of acetylcholine, dopamine, and serotonin. Lecithin—an acetylcholine precursor—and choline chloride have also been used, though with mixed results.

Vasoactive Intestinal Peptide

The expression of CD4 glycoprotein has been demonstrated in human brain (Pert et al. 1986). The cerebrum contained the highest receptor concentration, with the highest in the superficial layers, while the frontal lobes and perilimbic cortex also showed high concentrations, with the greatest density in hippocampus. HIV-1 gp120 envelope glycoprotein antagonizes the physiologic activity of VIP (Pert et al. 1988), which is secreted by glial cells and supports neuronal growth and maintenance (Brenneman and Eiden 1986). Inhibition of VIP binding to its endogenous ligand (the CD4 receptor) by binding of gp120 may explain how the pathophysiologic process in HAD may occur with only minimal direct neuronal infection by virus. Such a mechanism may dictate the utility of peptide T, an octapeptide that is homologous with the binding domain in the V2 region of the gp120 glycoprotein coat of HIV-1. Maps of CD4 receptor and gp120 binding are very similar, and therefore it has been proposed that oligopeptides related to peptide T could be used to inhibit gp120 binding in the CNS. In a related manner, the mechanism by which HIV-1 causes HAD has been attributed to the virus's homology with neuroleukin, required for cholinergic function and sensory neuron growth in vitro (Ho et al. 1987; Lee et al. 1987). Although it had been reported that peptide T reversed a loss of dendritic arborization induced by gp120 in culture, Pulliam and colleagues (1993) did not find that gp120 caused neuronal death in culture; they did, however, find evidence of astrocyte killing and alterations. gp120 has been found to induce apoptosis, which is a known indirect cause of neuronal cell death in HAD (Petito and Roberts 1995). Hence, peptide T itself may prove to be of therapeutic value, and another possible avenue

of drug development in HAD may include inhibitors of virus binding, complementing reverse transcriptase inhibitors (e.g., zidovudine, didanosine, zalcitabine, stavudine, 3TC, nevirapine, and atevirdine) as well as the protease inhibitors (e.g., saquinavir).

Other Cofactors Implicated in the Pathophysiology of MCMD and HAD

Viral Co-infections

HAD is described as a diagnosis of exclusion of opportunistic infections and neoplasms of the CNS, since each of these alone could account for cognitive impairment (American Academy of Neurology 1991). Still, viral co-infection does occur in brain and has been discussed as an important potential cofactor in potentiating HAD (e.g., as in the case of CMV co-infection discussed earlier in this chapter). This potentiation might occur directly by deficits caused by the virus involved and indirectly by stimulation of brain macrophages with resultant increases in HIV-1 replication.

At the University of Miami Comprehensive Drug Research Center, there was a threefold increase in mortality rate at follow-up among HIV-1-seropositive substance users co-infected with HTLV-I and/or HTLV-II (Page et al. 1990). Although these infections were later specified to be predominantly due to HTLV-II—a T cell lymphotropic retrovirus type not strongly associated with clinical sequelae—an ataxic neuropathy has been related to this virus (Sheremata et al. 1993). The patients observed presented with a prominent ataxia along with altered mental status, both of which are associated with HAD. Of note, injecting substance users in Europe have been noted to be at increased risk for HAD (Chiesi et al. 1996). Hence, both HTLV-I (well known to be associated with CNS lymphoma) and HTLV-II co-infections may increase the likelihood of HAD.

Similarly, PML is caused by a papovavirus (JC polyomavirus) infection and, as previously noted, may be difficult to distinguish

from HAD. The virus causes a lytic infection of oligodendrocytes and demyelination, and its effects may thereby synergize with the demyelinating effects of HIV-1 in the pathogenesis of this dementia. PML is currently virtually untreatable and carries a poor prognosis, though high-dose zidovudine has been applied with some success (Singer et al. 1994a), as well as IL-2, interferon-α, cidofovir, peptide T, and topotecan. A few cases of partial remission have been reported that are uncharacteristic of this disease outside of HIV-1 infection. Herpes simplex virus also presents as a co-infection with HIV-1. In the vast majority of these cases, it is herpes simplex virus–1 (HSV-1), which has a strong predilection for the subfrontal and mesial temporal lobes and can be treated with intravenous acyclovir. Epstein-Barr virus (EBV) co-infection is quite common in AIDS and may be a very infrequent cause of encephalitis (as well as a potentiator of immunologic progression in the periphery).

Nonviral Co-infections

Nonviral co-infections of the CNS may also occur and should be screened for prior to any diagnosis of MCMD or HAD. The most common of these is toxoplasmosis, a protozoal infection occurring in 15% to 30% of AIDS patients. Patients with CNS toxoplasmosis frequently present with multiple ring enhancing lesions on CT scan with iodinated contrast. Toxoplasmosis is the CNS infection most responsive to treatment, which is accomplished with pyrimethamine and sulfadiazine (Pons et al. 1988); trimethoprim/sulfamethoxazole may be effective in its prophylaxis, as well as providing concurrent prophylaxis against *Pneumocystis carinii* pneumonia (Goodkin 1995b).

Cryptococcosis, a fungal infection, is the next most frequent nonviral infection and is seen in up to 12% of AIDS patients. Like HIV-1, cryptococcosis may present with an organic manic syndrome (Johannessen and Wilson 1988). CSF examination is crucial to this diagnosis, with India ink preparation, cryptococcal antigen, and fungal culture tests being the mainstays. Treatment is with amphotericin B alone or in conjunction with flucytosine, fluconazole, or itraconazole.

Other nonviral infections of brain include tuberculosis (TB), atypical TB infections (infection with *Mycobacterium avium-intracellulare*) (though rare in the CNS), other fungal infections (candidiasis, aspergillosis, mucormycosis, histoplasmosis, and coccidioidomycosis), and bacterial infections (listeriosis, nocardiosis, *Escherichia coli* infection), and neurosyphilis. Of note, patients with neurosyphilis may present with an organic manic syndrome. Neurosyphilis has also been indicated to be underdiagnosed in the setting of HIV-1 infection (Katz and Berger 1989). Although how to screen and establish this diagnosis remains an unsettled clinical problem of some controversy in HIV-1 infection, we recommend that all HIV-1-seropositive patients suspected of cognitive impairment be screened with CSF by means of both the VDRL and the fluorescent treponemal antibody (FTA) absorption test, since patients with a history of syphilis may lose reactivity in serum in the setting of HIV-1 infection (even when they are asymptomatic for HIV-1). Moreover, neurosyphilis itself may be asymptomatic in about 10% of cases (Katz and Berger 1989). Treatment consists of intravenous aqueous penicillin G or intramuscular procaine penicillin G, supplemented by probenecid, administered for 10 days.

Neoplasms of the CNS are another cause of encephalopathy that may resemble HAD. Although Kaposi's sarcoma is rare in the CNS, primary CNS lymphoma is second only to toxoplasmosis as a source of intracranial mass lesions (So et al. 1988). Radiation therapy is the primary treatment for CNS neoplasms.

Metabolic sources of encephalopathy must also be ruled out in any patient with MCMD or HAD, although, like the other aforementioned infectious diseases, these conditions may coexist with HAD over time and influence its expression. A pulmonic source, with hypoxemia, is particularly important to rule out, since this is commonly the result of *P. carinii* pneumonia—the most frequent cause of death in patients with AIDS prior to successful primary prophylaxis and still a common cause of death in those with a CD4 cell count of fewer than 50 cells/mm^3. Hepatic (e.g., hepatitis A, B, or C viruses), renal (e.g., HIV-1 nephropathy), and gastrointestinal (e.g., CMV colitis, cryptosporidiosis diarrhea) sources must also be considered.

Psychoneurotoxicity of Prescribed Medications and Other Therapies

Toxicity as a cause of encephalopathy must be considered as well. Zidovudine itself has been shown to induce an organic manic syndrome responsive to lithium treatment (O'Dowd and McKegney 1988). This iatrogenic source is especially important to investigate, since high-dose zidovudine is frequently used as a treatment for HAD. Other sources to consider are interferon-α (disorientation, slowness, hallucinations) (see Pavol et al. 1995; Saphier 1994); vidarabine (ara-A) (confusion, visual hallucinations, mutism) (Cullis and Cushing 1984); compound Q (disorientation, coma); pentamidine (severe hypoglycemia or hypotension with depressed mental status) (Ochitill and Dilley 1988); metronidazole (dizziness, confusion); acyclovir (confusion, agitation, hallucinations); amphotericin B (disorientation, lethargy); antineoplastic drugs such as vincristine and procarbazine (disorientation, confusion); steroids, both catabolic and anabolic (mania, depression); and radiation therapy, for both acute and delayed reactions (cognitive impairment).

Dietary Factors

Diet has also been implicated as a possible cofactor in HIV-1-induced neuropsychological deficits (see Chapter 7). The possible potentiation of HAD by deficiencies in vitamins B_6, $B_{12,}$ and E has already been discussed. The pathology of the myelopathy produced by vitamin B_{12} deficiency is similar to the vacuolar myelopathy caused by HIV-1 (Kieburtz et al. 1991b). It has been reported that CSF vitamin B_{12} level is more sensitive than serum level and may be useful when clinical monitoring of this deficiency is required.

Another potential dietary factor may be zinc intake. Zinc deficiency has been associated with more rapid general clinical progression of HIV disease (Fabris et al. 1988), and zinc has been observed to block the action of NMDA on cortical neurons (Peters et al. 1987). Hence, zinc supplementation may be helpful in the pre-

vention of general clinical progression as well as CNS progression of HIV-1 infection. However, it has been demonstrated that inhibition of seizures by γ-aminobutyric acid (GABA) may be decreased by zinc released from mossy fiber terminals of granule cells seen in human temporal lobe epilepsy (Buhl et al. 1996). Though this effect is part of a pathologic process, it must be cautioned that zinc supplementation may carry the possibility of toxic as well as therapeutic effects. This same argument might apply to the other dietary factors discussed; specific clinical recommendations for the treatment of deficiencies of these nutrients and, possibly, for the protective effects of supplementation await randomized, controlled clinical trials.

Implications for Psychoneuroimmunologic Associations

A spectrum of CNS clinical disease has been described in HIV-1-seropositive individuals. The course of CNS disease progression in these individuals generally is slow and spans more than 10 years. A considerable degree of viral propagation in the CNS occurs prior to testable neuropsychological impairment, MCMD, and HAD. The onset and progression of MCMD and HAD represent, at least in part, a direct virologic mechanism (see Figure 8–1 earlier in this chapter).

The latency or slow progression of HIV-1 infection in the brain appears to be partially independent of progression of the disease in the periphery, especially over the long period in which BBB integrity is maintained, as has been pointed out earlier in this chapter, with particular reference to the effects of the proinflammatory cytokines, the neurotrophic cytokines, and Th1 versus Th2 cytokines. The fact that psychoneuroimmunology research has shown that life stressors may decrease levels of Th1 cytokines—for example, IL-2 (Th1 and neurotrophic) (Glaser et al. 1990)—and interferon (Palmblad et al. 1976) and increase proinflammatory cytokine levels—for example, levels of IL-1β (Maes et al. 1993) and IL-6 described in major depressive disorder and of TNF-α after

traumatic stressors (Dekaris et al. 1993)—does not always have parallel implications for CNS HIV-1 progression. That is, whereas decrements in IL-2 and increments in IL-1β, IL-6, and TNF-α as well as in interferon-α would be suspected to be deleterious in the CNS and the periphery, decrements in interferon-γ would not show such a parallel effect. Thus, future psychoneuroimmunology studies should identify CNS HIV-1 progression along with peripheral progression. Studies that include cytokine levels should examine both the serum and the CSF in order to differentiate effects of the same behavioral factors in these two compartments.

Substantia Nigra

A predisposition of HIV-1 to affect a specific brain site—the substantia nigra—was noted in terms of early clinically defined motor findings associated with parkinsonism as well as with lowered CSF levels of dopamine. Regarding psychoneuroimmunology, behavior, and parkinsonian motor symptoms upon cocaine abstention, high levels of cocaine are associated with decrements in T lymphocyte proliferation to mitogen (Klein et al. 1988). Abstinence following cocaine abuse or dependence is associated with acute decreases in dopaminergic transmission (previously enhanced by the cocaine) and may predispose to progression of HIV-1 infection in brain by increasing the impact of HIV-1 itself on dopaminergic neuronal cell loss (Goodkin et al. 1998). In an attempt to maintain abstinence, dopaminergic agonists have been promulgated for the treatment of withdrawal, including drug cravings. Of note here is that whereas depressive symptoms are not specifically thought to be part of HAD, apathy, lethargy, and social withdrawal are. This symptom triad may specifically relate to deficits in dopaminergic transmission thought to underlie the phenomenology of "reward."

Given that dopaminergic agonists (e.g., pramipexole) are also expected to be efficacious in deterring the clinical effects of HIV-1-induced substantia nigra degeneration, two issues could be addressed simultaneously in the treatment of an HIV-1-infected cocaine user. First, withdrawal, if untreated, may be a risk factor for further HIV-1-induced CNS destruction, since neurons already

stressed by the infection would be further challenged by a lack of the stimulatory effects of a substance (cocaine) for which some level of accommodation had been achieved (Goodkin et al. 1998). Second, successful abstinence may restore use-associated decrements in T lymphocyte proliferation and is likely to promote more active coping strategies in response to life stressors to replace passive coping strategies such as substance use. Of relevance here, the use of active coping strategies was shown to be associated with higher CD4 cell counts and NK cell cytotoxicity in HIV-1 infected individuals (Goodkin et al. 1992a, 1992b).

Raphe Nuclei

In a similar fashion, decrements in CSF 5-HIAA indicate a susceptibility of serotonergic neurons to HIV-1 in a second brain site, the raphe nuclei. Major depressive disorder, which would affect such nuclei, decreases available serotonin, at least in some cases. Hence, this disorder might render these neurons especially vulnerable to HIV-1 infection, which could directly or indirectly affect these nuclei. Hence, the SSRIs and vitamin B_6 may have a role in the development of a comprehensive treatment regimen, as may dopamine agonists.

In terms of psychoneuroimmunology, the utility of one SSRI—fluoxetine—has been suggested in the treatment of chronic fatigue syndrome (also referred to as "low NK syndrome") (Klimas et al. 1993). On a related note, fatigue in an HIV-1 infected individual sometimes represents a constitutional symptom associated with HIV-1 disease progression. Because of the psychoneuroimmunologic effects of major depressive disorder (e.g., in decreasing NK cell cytotoxicity), an aggressive approach to treatment using, for example, the SSRIs may be warranted with HIV-1-infected patients.

Hippocampus

A third brain site for psychoneuroimmunologic interactions of importance with behavior—the hippocampus—should be discussed

(see Chapter 7, this volume). The hippocampus is the most rostral portion of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis and is one of the sites in brain with the highest concentration of CD4 receptor. Hence, as pointed out in the chapter on cognition in HIV-1 infection (see Chapter 7), chronic stressors, aging, and major depressive disorder might interact with HIV-1 infection centrally to the extent that the hippocampus is predominantly affected because of neuronal destruction associated with chronically high levels of glucocorticoid release and the high density of glucocorticoid receptors in the hippocampus. Such effects might also be specifically demonstrable by neuropsychological testing for verbal memory, since the hippocampus is a major site of information retrieval.

In terms of psychoneuroimmunology, an important aspect of the implications of these neuroimmunologic effects is that CNS HIV-1 infection itself constitutes a significant life stressor. This proves to be especially true in the earlier clinical stages of HIV-1 infection, when consciousness of one's own neuropsychological performance is still quite intact. To this extent, then, cognitive impairment is yet another stressor in the litany faced by the HIV-1-infected population, which could contribute to chronically elevated serum cortisol levels. As pointed out earlier in this chapter, such cortisol increments are now suspected to be closely related to peripheral progression of HIV-1 infection, since cortisol is associated with decrements in Th1 cytokines, increments in Th2 cytokines, induction of apoptosis, and increase in transcription of HIV-1 proteins (Clerici et al. 1994). In fact, it has been known for some time that hydrocortisone increases the ability to productively infect normal peripheral blood mononuclear cells as well as those from patients with early symptomatic HIV-1 infection and AIDS (Markham et al. 1986). This work suggests that one focus of future research in psychoneuroimmunology should involve measurement of CSF CRH levels in association with neuropsychological impairment and life stressors and examination of the progression of HIV-1 peripherally in terms of CDC stage change, the development of AIDS, and death.

Conclusion

An integration of brain, immune system, and behavior in HIV-1 infection must address the implications of the research reported in this chapter in relation to a final common pathway to outcome—viral burden. However, it is not yet known how this burden should be measured to best reflect tissue damage. Possible candidates include load of CSF HIV-1 proviral DNA, HIV-1 RNA, p24 core antigen, and gp120—or some combination of these. It may prove necessary to quantify viral burden from brain tissue sites to obtain a measure that corresponds to tissue damage—an approach that greatly limits clinical utility.

Viral burden in three especially relevant brain sites has been described in this chapter: the substantia nigra, raphe nuclei, and hippocampus. Specific neurohormones are associated with each of these brain sites: dopamine with substantia nigra, serotonin with the raphe nuclei, and glucocorticoids with the hippocampus. The last-mentioned region may represent a site for regulation of the HPA axis, since high densities of both glucocorticoid and CD4 receptors are found there. As noted earlier, the relevance of this brain site highlights the importance of cortisol in the interactions among psychosocial factors, the brain, and viral burden.

Cortisol was one of the first neuroendocrines described to be important in mediating relationships between psychosocial status and the immune system. Since that time, numerous other neuroendocrines have been demonstrated to be significant in determining these relationships as well: norepinephrine, epinephrine, neuropeptide Y, growth hormone, prolactin, endogenous opioids, and substance P, among others. Nevertheless, in HIV-1 infection, a renewed focus on cortisol in psychoneuroimmunologic relationships is indicated by the data related to the progress of this disease and the CNS mediation of the interactions among psychosocial status (the LHPA axis), the brain (hippocampus), neuropsychological impairment eventuating in HIV-1-associated dementia (deficits in verbal memory), and viral burden (high density of CD4 receptor—sites for gp120 binding). Further, measures of host immune response— that is, proinflammatory, neurotrophic, and Th1 versus Th2 cytokine

levels—are interrelated with viral burden.

Behavioral and pharmacologic treatments based on the implications summarized here represent a significant clinical contribution to the lives of HIV-1-infected individuals in that they may reduce the likelihood of the development of HAD as well as modulate interactions between life stressors and other psychosocial factors on brain, immune system, and progression of the disease in the periphery. Research on such treatments integrating these factors is required that will differentiate central from peripheral effects on HIV-1. Since central and peripheral effects of HIV-1 are known to be regulated differently, a greater focus on the macrophage, rather than on T lymphocytes, is needed in research addressing central disease progression.

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Chapter 9

Stress Management and Psychosocial Predictors of Disease Course in HIV-1 Infection

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Individuals with seropositivity for human immunodeficiency virus–1 (HIV-1) are faced with a wide variety of stressors. Given the highly stressful circumstances under which these individuals live, we reasoned that stress management interventions may help them manage this stress. As such, these interventions represent an effort at secondary prevention, helping to prevent further deterioration and enhance quality of life. We furthered reasoned that behavioral interventions that enhance personal control over one's reaction to life stressors, increase recruitment of social support, and encourage the use of active coping strategies may reduce the deleterious affective and behavioral sequelae of HIV-1 infection.

Our first effort at systematically implementing such interventions began in 1986 in a program designed to buffer the initial impact of an HIV-1-seropositive diagnosis in homosexual men. We first examined the short-term effects of two stress management interventions as buffers of the depression (and immunologic changes) that follows HIV-1 serostatus notification: cognitive-behavioral stress management (CBSM) and aerobic exercise training. We next examined the effects of these interventions on various

psychological variables (distress, coping, social isolation), as well as immune measures, including antibody titers to two herpesviruses, in this cohort. We then examined psychological predictors of disease progression 2 years after entry into the study.

More recently, we have examined the effectiveness of CBSM in men who have already progressed to early symptomatic HIV-1 infection. In this chapter, we present the theoretical rationale for how the CBSM intervention might affect the immune system, the content of the interventions, and the major findings from our study. Although the primary focus in this chapter is on the cognitive-behavioral intervention (i.e., CBSM), we also present major results for the aerobic exercise/training intervention. A review of other psychoneuroimmunologic stress management programs in HIV-1-infected populations, as well as psychological factors in HIV-1 infection relevant to psychoneuroimmunology, can be found in the discussion section, where we integrate the findings in the literature with our findings.

Stressors and Affective Distress in HIV-1 Infection

Homosexual men who are infected with HIV-1 face a multitude of stressors. As HIV-1 infection progresses, they are faced with changes in health and job status, worries about the continuance of health insurance, mounting medical costs, and deterioration in quality of life and ability to care for oneself. Many may face the death of friends or their partner from HIV-1 and experience homophobic responses of friends and family, leading to a further sense of social isolation (Blendon and Donelan 1988). Affective distress is high in this population, with depression, particularly adjustment disorder with depressed mood, present in as many as 80% of patients (Goodkin 1988). The suicide rate among HIV-1-infected men has been reported to be 36 times that among age-matched uninfected men (Marzuk et al. 1988). HIV-1-infected individuals experience high levels of anxiety, especially during the prodromal phase of the illness and as symptoms indicative of disease progression

appear (Atkinson et al. 1988; Nichols 1983).

Knowing what is potentially in store makes receiving a diagnosis of HIV-1 seropositivity a stressful event (Hoffman 1991). The incidence of DSM-III-R (American Psychiatric Association 1987) Axis I affective (mood and anxiety) and adjustment disorders and distress level are known to be elevated after seropositivity notification (Jacobsen et al. 1990; Perry et al. 1992; Rundell et al. 1988). In fact, fear of overwhelming distress following positive status notification is the most common reason for not getting tested among individuals who are at risk for HIV-1 infection (Lyter et al. 1987).

Because finding out one's seropositive status was thought to be the first very stressful event in a potential series of events confronting HIV-1-seropositive individuals, our research group at the University of Miami felt stress management interventions might provide some benefit. On the basis of the available literature, we hypothesized that stress management interventions would afford protection against both psychological and immunologic sequelae of seropositivity notification. Interestingly, Namir (1986) reported that 81% of HIV-1-infected respondents expressed an interest in individual or group psychological intervention, though only 28% were receiving any. In addition to elevated distress, the coexistence of feelings of life-threat, doom, anger, and responsibility for making immediate lifestyle changes after a seropositive diagnosis (Christ and Wiener 1985; Kaisch and Anton-Culver 1989; Viney et al. 1989) suggested that interventions that provide support, teach coping strategies, and offer the opportunity for mastery experiences might be beneficial. Such interventions could also help these individuals to ventilate feelings such as anger and depression (Miller 1988) and to manage anticipatory grief over the expectation of loss and death of self and others (Cohen 1990; Pickrel 1989). All of these putative intervention effects seemed likely to be facilitated with a group treatment format.

Theoretical Background

The theory that our group follows has been described in detail elsewhere (Antoni et al. 1990b). In this theory, we hypothesize that

stressors and negative affective states lead to sympathetic arousal and activation of the limbic-hypothalamic- pituitary-adrenal (LHPA) axis, which in turn could lead to down-regulation of the immune system and more rapid disease progression.

Stressors, Distress, and Immunity

A number of stressors, several of which are directly relevant to men infected with HIV-1, have been associated with decrements in immune function:

- Loss associated with bereavement (Bartrop et al. 1977; Irwin et al. 1987a, 1987b; Linn et al. 1981)
- Loss after a natural disaster (Ironson et al. 1997)
- Being a caregiver (e.g., for individual with Alzheimer's disease) (Kiecolt-Glaser et al. 1987b)
- Break-up of a relationship (e.g., divorce) (Kiecolt-Glaser et al. 1987a)
- Being in a poor-quality marriage (Kiecolt-Glaser et al. 1987a, 1988)

Immune decrements most often associated with these stressor effects are most consistently decrements in functional measures associated with cellular immunity. These include, but are not limited to, decrements in response to mitogens, such as blastogenic response to phytohemagglutinin and pokeweed mitogens (Bartrop et al. 1977; Linn et al. 1981; Kiecolt-Glaser et al. 1987a), decreased natural killer (NK) cell activity (Irwin et al. 1990a; Levy et al. 1987), and increased titers to Epstein Barr virus (EBV) (Glaser et al. 1991). In addition, several studies have noted decrements in phenotypic immune measures: CD4+ T helper lymphocytes, CD4/CD8 (helper/suppressor) cell ratios (Kiecolt-Glaser et al. 1987b), CD8+ suppressor/cytotoxic T (T_8) lymphocytes (McKinnon et al. 1989), and NK cells (Kiecolt-Glaser et al. 1987a; McKinnon et al. 1989). Herbert and Cohen (1993) provide an excellent review of stressor effects on the immune system.

In addition, affective states often associated with stressors, such as depression (Calabrese et al. 1987; Irwin et al. 1990b), loneliness (Kiecolt-Glaser et al. 1984), and anxiety (Ironson et al. 1990, 1994, 1997; Linn et al. 1981), have also been associated with decrements in immune function. Impaired NK cell cytotoxicity appears to be the most commonly observed immunologic correlate of depressed affect and major depressive disorder (Irwin et al. 1990a; Stein et al. 1991). However, Schleifer and colleagues (1989) found an age-by-depression interaction effect. Irwin and colleagues (1990b) found that exposure to threatening life events was associated with a 50% reduction in NK cell cytotoxicity in a group of healthy, non-depressed subjects, which suggests that distress, as well as depression, may be associated with immunologic changes.

Possible Mechanisms of Stressor-Immune Relationships

Several mechanisms involving nervous system and endocrine pathways have been proposed for explaining how stressors and distress affect immune function. Neuroendocrine mediation could occur through activation of either the LHPA axis or the sympathetic adrenomedullary system. The LHPA axis may be disrupted at several levels in major depressive illness and other affective distress states (Amsterdam et al. 1989). Several of these LHPA axis abnormalities gradually normalize with clinical improvement in depression (Amsterdam et al. 1985; Greden et al. 1983).

Because immunologic function is impaired by cortisol in humans (Cupps and Fauci 1982; Munck et al. 1984), immunologic correlates (especially blastogenesis and NK cell cytotoxicity) of depressed states have been studied extensively. It has been shown that glucocorticoids, a product of the LHPA axis, 1) enhance HIV-1 replication (Markham et al. 1986), 2) are immunosuppressive (Cupps and Fauci 1982), and 3) accompany affective disorders (Gold et al. 1986) and stressful experiences (Borysenko and Borysenko 1982; Jacobs et al. 1986).

A separate but related neuroendocrine response system, the sympathetic adrenomedullary system, is activated during stressful

circumstances, and the catecholamines norepinephrine and epinephrine are released. There are direct neuronal links between the sympathetic nervous system and lymphoid tissue (Felten et al. 1985), and lymphocytes have β receptors (Plaut 1987) (which, in general, respond to catecholamines). Behavioral stressors may induce AMP-mediated suppression of lymphocyte and NK cell function (Plaut 1987), and epinephrine administration has been shown to be directly related to a decrease in mitogen proliferative response (Crary et al. 1983). Activation of both the LHPA axis and the sympathetic adrenomedullary system, which may interact (Axelrod and Reisine 1984), during exposure to chronic uncontrollable stressors adversely affects immunologic status (Cupps and Fauci 1982; Roszman et al. 1985).

Additional mechanisms may be operating in aerobic exercise and training. Regular exercise has been shown to be associated with decreased depression and anxiety and increased self-esteem (Morgan 1982, 1984, 1985). It has also been associated with a decrease in heart rate, thought to be the result of a decrease in sympathetic activity accompanied by an increase in parasympathetic activity (Frick et al. 1967). In addition, opioid peptides such as met-enkephalins and β-endorphins, which are thought to increase in exercise (Carr et al. 1981), have been shown to be associated with improvements in mitogen proliferative responses and regression of Kaposi's sarcoma lesions in AIDS patients (cf. Wybran et al. 1987).

Intervention Impact According to Our Theoretical Approach

The neuroendocrine patterns described in the previous subsection may be engaged when an individual is exposed to uncontrollable chronic stressors, has inadequate social support, and uses denial or avoidance coping strategies (Antoni et al. 1990b). If depression and uncontrollable stressors are associated with impaired immunologic function mediated by neuroendocrine changes in HIV-1-infected individuals, and if intervention-associated decreases in depressed mood, through either CBSM or exercise, help to normal-

ize neuroendocrine function and sympathetic activation in this population, then such interventions may concurrently act to attenuate neuroendocrine-associated immunosuppression. Therefore, we hypothesized that intervention-associated decreases in depressed affect and distress would reduce urinary cortisol and catecholamine levels and, possibly, normalize distress and immunologic impairments associated with depression.

Stress Management and Exercise Interventions

Stress Management and Relaxation Training Program

The Stress Management and Relaxation Training (SMART) program is a 10-week program with two major components: a stress management component that is partly didactic but also includes group sharing of emotions and experiences, and a relaxation training component that involves instruction and practice through a variety of experiential exercises. The stress management and relaxation techniques used in this program, which are highlighted in Table 9–1, include anxiety reduction procedures (e.g., progressive muscle relaxation and relaxing imagery), cognitive coping skills training (e.g., cognitive restructuring, emotion-focused and problem-solving strategies), and social support enrichment (social network sensitization and utilization). More recently, we have added a component directed at adherence to antiretroviral medications. This is especially important for those taking triple or quadruple drug regimens, because missing doses can lead to resistance. Intervention group members met once or twice weekly over the 10-week period in groups of five to eight, led by two cotherapists.

To maximize the effectiveness of this intervention with the target population, we encouraged subjects to generate examples of recent psychosocial stressors to use in in-session behavioral role-plays. Each treatment component was adapted for use with the study population. Relevant issues such as immune system functioning, viral transmission, safer sex, and medical treatments

Table 9–1. Components of the University of Miami Stress Management and Relaxation Training (SMART) program

Cognitive-behavioral stress management (CBSM)

1. Awareness of stress, stressors, and stress reactions
2. Recognition of negative self-talk and automatic thought patterns
3. Cognitive restructuring: rational thought replacement
4. Development of adaptive coping strategies for managing stress (direct and indirect); identification of problem-focused and emotion-focused strategies
5. Dealing with difficult emotions such as anger
6. Assertiveness and development of negotiation skills
7. Use and maintenance of social support; group sharing
8. Information on HIV infection, healthy lifestyles, and safer sex

Relaxation

1. Progressive muscle relaxation
2. Deep, slow, diaphragmatic (abdominal) breathing
3. Guided visualization (using a relaxing beach scene or self-developed relaxing scene)
4. Autogenic training
5. Meditation (using a mantra or breath as a focus)

for symptoms were introduced for educational purposes and as catalysts for discussion and application of CBSM techniques.

CBSM may enhance psychological functioning in stressed individuals by 1) modifying appraisals of stressors and providing the host with an available coping response (Folkman et al. 1991; Turk et al. 1986); 2) changing maladaptive cognitive distortions (Simons et al. 1984); 3) decreasing hopeless thoughts (Rush et al. 1982); 4) increasing perceptions of self-efficacy, personal control, and mastery (Fishman and Loscalzo 1987); and 5) increasing the availability and utilization of social support networks (Vachon et al. 1980). The specific CBSM intervention used in our program is tailored to address the issues of loss of personal control, coping demands, social isolation, and depression—all of which are salient for HIV-1-infected individuals. As such, the CBSM intervention may both enhance

well-being across affective, cognitive, and social spheres of functioning and arm participants with several prophylactic "stress buffers."

In addition, the group format may provide a sense of universality and allow HIV-1-infected individuals to express their feelings and learn successful styles of coping employed by other group members (Spiegel et al. 1981; Yalom and Greaves 1977). In one study, men diagnosed with AIDS and men with HIV-1 seropositivity perceived peers to be the most helpful source of social support; family members were less likely sought and were perceived as least helpful (Hays et al. 1990). Multimodal stress management interventions that improve cognitive and social/interpersonal coping strategies may be especially useful in reducing distress and depression among HIV-1-infected individuals and may also help them to adopt and maintain necessary lifestyle changes.

Exercise Protocol

Subjects exercised three times a week for 45 minutes of interval training on a bicycle ergometer. Interval training consisted of repeated 3-minute bouts of exercise at approximately 80% of a subject's predicted maximum heart rate (PMHR) (i.e., 220 minus the subject's age) alternating with 2-minute periods of less intense exercise (60%–79% of the PMHR).

Stressor of HIV-1 Serostatus Notification

Psychological and Immune Measures

Our initial cohort consisted of healthy gay men between the ages of 18 and 40 who had never been tested for HIV-1 antibodies and presented no clinical signs or symptoms of HIV-1 infection on physical examination. (Subject inclusion and exclusion criteria are covered elsewhere [Ironson et al. 1990].) Baseline immunologic comparisons conducted 5 weeks before the men were tested for and notified of their antibody status indicated that those shown ul-

timately to have a positive HIV-1 serostatus showed significantly lower CD4 cell counts (as would be expected) and lower proliferative responses to phytohemagglutinin and pokeweed mitogen, as compared with the laboratory control subjects (Klimas et al. 1991). Although the HIV-1-seropositive men showed a significant increase in state anxiety and intrusive thoughts on receiving news of a seropositive test, the only immune measure that decreased significantly was NK cell cytotoxicity; these changes were significantly correlated with increases in anxiety (Ironson et al. 1990). However, there were no changes in either CD4 cell counts or mitogen responses, contrary to what one might expect with the stress-immune model. One possible explanation for this is that HIV-1-seropositive men have a dampened immune response, at least for some immune measures. Both anxiety and intrusive and avoidant thoughts returned to baseline levels by the end of the study, 5 weeks later.

Those men shown ultimately to have a negative HIV-1 serostatus showed significantly lower NK cell cytotoxicity and proliferative responses to phytohemagglutinin and pokeweed mitogen compared with the laboratory control subjects at entry to the study (Klimas et al. 1991). This suggests that HIV-1-seronegative men may have had suppressed cell-mediated immune function as a result of either being in a risk group or experiencing the anticipatory stressor of impending serostatus notification. A focused analysis of this 5-week prenotification period revealed that the HIV-1-seronegative men, although showing the depressed phytohemagglutinin and pokeweed mitogen responses at study entry, showed a recovery of blastogenic responses (to laboratory normal values) 5 weeks later, after learning of their HIV-1 seronegative status (Ironson et al. 1990). These changes suggest that the decision to learn their serostatus and thereby confront their perceived risk of infection was functioning as an acute psychosocial stressor.

Neurohormonal Correlates

To examine the degree to which changes in neurohormonal variables mediated these phenomena, we assessed plasma levels of

cortisol, severity of intrusive thoughts, and several measures of affective distress among the HIV-1-seronegative men at baseline and 5 weeks later. Cortisol levels were found to be elevated at baseline, at values similar to those found in subjects exposed to laboratory psychological stressors (Kuhn 1989; Williams et al. 1982) and bereaved individuals (Irwin et al. 1987a, 1987b). Cortisol concentrations receded to levels of same-aged healthy individuals at rest (Meyerhoff et al. 1988) across the 5-week period, a pattern mirroring the changes in mitogen response during this same period. Higher cortisol values at baseline were associated with lower phytohemagglutinin (but not pokeweed mitogen) values and higher levels of depression, confusion, and anxiety both at baseline and 5 weeks later (Antoni et al. 1990a).

Persisting intrusive thoughts about risk of AIDS (after seronegative status notification) were consistently associated with higher cortisol levels. Because cortisol secretion is known to rise in anticipation of uncontrollable environmental stressors (Weiss 1972) and to be elevated in states of affective distress (Amsterdam et al. 1989), we reasoned that the stressor of entering in this study and agreeing to have one's serostatus denoted may have had a transient immunologic effect mediated by psychological distress and/or plasma cortisol elevations (Antoni et al. 1990a). It is noteworthy that we found very different patterns of plasma cortisol change over the study period for HIV-1-seropositive men, and this suggests that HIV-1 infection alters neuroendocrine responses and/or neuroendocrine-immune associations (Antoni et al. 1991b). However, plasma cortisol samples, even when collected in the early morning, are subject to secretory bursts that may present a distorted picture of the individual's chronic basal level; thus, these apparent serostatus differences are rendered inconclusive and not necessarily applicable to chronic stressors or disease states. Urinary cortisol and cateholamine levels are believed to offer more integrated measures of neuroendocrine levels during exposure to sustained life stressors (e.g., having symptomatic HIV-1 infection) and are thus being measured in our current protocol.

Buffering Effect of Stress Management/ Relaxation Training and Aerobic Exercise Training

Because improvements in aerobic fitness levels achieved in structured exercise programs and in CBSM have been shown to be related to reductions in anxiety and depression (Greist et al. 1979; Morgan 1984) and increases in self-esteem and feelings of well-being (Morgan 1982, 1985), we examined the effects of these interventions on the distressing effects of HIV-1 serostatus notification. Sixty-five homosexual men were randomly assigned to either a group exercise program (one that used bicycle ergonometry), group CBSM, or an assessment-only control condition.

Psychological Effects

Psychological distress measures and immune markers were collected after 5 weeks of training (72 hours prior to serostatus notification) and again 1 week after notification. Control group members found to be HIV-1-seropositive showed significant increases in anxiety and depression after notification, whereas HIV-1-seropositive exercisers showed no changes on these measures and actually resembled individuals in the HIV-1-seronegative groups (LaPerriere et al. 1990). The HIV-1-seropositive subjects in the CBSM group showed no significant changes in anxiety or depression scores on the Profile of Mood States (POMS; McNair et al. 1971), and postnotification values for depression in this group were just above college student norms, a pattern very similar to the results reported for the aerobic exercise intervention (Antoni et al. 1991a). Finally, relaxation practice was significantly correlated with lower POMS anxiety and depression scores (postnotification) after control for prenotification distress levels.

Effects on Immune Status

We observed that HIV-1-seropositive control subjects showed slight decrements in response to phytohemagglutinin, NK cell cytotoxicity, and CD56+ cell counts between pre- and postnotification (with no change in CD4 cell counts). In contrast, HIV-1-seropositive subjects in the CBSM group displayed significant increases in CD4 and NK cell counts and slight increases in phytohemagglutinin response and

NK cell cytotoxicity over a similar period (Antoni et al. 1991a).

In addition, we noted that greater frequency of home relaxation practice over the initial 5 weeks of the study was correlated with higher numbers of CD4+ and CD56+ cells. Continued relaxation practice during the acute notification period (weeks 5 to 7) was also positively correlated with these immune measures. Aerobic exercise/training had a similar buffering effect on several immune measures: no significant change in CD4+ cell count, CD56+ cell count, or NK cell cytotoxicity was found in seropositive exercisers (LaPerriere et al. 1990). However, the interaction for CD56+ cells reached significance (no change in the exercisers, but decrease in the control subjects).

Effects of the Ten-Week Intervention

CBSM Effects on Adjustment to HIV-1 Infection: Coping and Social Support

Together, our studies thus far suggested that 1) HIV-1 serostatus testing is associated with affective, neuroendocrine, and immunologic changes consistent with an acute, uncontrollable stressor, and 2) behavioral interventions may attenuate the effects of this stressor on distress levels (and immunologic correlates) during the short-term impact period after HIV-1 serostatus. We also studied CBSM intervention effects over the 5-week adjustment period following the diagnosis. Because this intervention provided subjects with alternative cognitive and behavioral coping strategies for dealing with stressors and did so in a supportive group environment, we hypothesized that intervention group members would show increases in adaptive coping strategies and decreases in maladaptive strategies such as denial, disengagement, and substance use. We also hypothesized that they would report higher levels of social support and greater use of coping strategies involving the enlistment of support networks than would the HIV-1-seropositive men in the control group.

Men in the control group showed significant decrements in social support (as measured by the Social Provisions Scale [Cutrona

and Russell 1987]) and decreases in seeking instrumental and emotional social support as coping strategies over the 5 weeks of the initial adjustment period. In contrast, the men in the CBSM group maintained their social support levels and social support–seeking coping strategies (Friedman et al. 1991). A third group, included for comparison, comprised asymptomatic HIV-1-seropositive homosexual men who already knew their diagnosis at baseline. As expected, the pattern of CBSM effects for these men was similar to the pattern shown by those who learned their diagnosis across the intervention—and the two groups had similar changes on several active/involvement coping measures (active coping, planning and acceptance)—but showed significant 10-week increases rather than merely a buffering of decrements, as had been noted in the diagnosis notification groups. The men in the CBSM group also showed significant decreases in behavioral disengagement, denial, and mental disengagement during this period (Antoni et al. 1992). These findings suggest that the 10-week stress management intervention may buffer the stressor of notification of HIV-1 seropositivity by maintaining or enhancing social support levels and enhancing use of adaptive coping strategies.

CBSM and Aerobic Exercise/Training Effects on Epstein-Barr Virus and Other Herpesvirus Antibody Titers

Because our previous work suggested that psychosocial stressors and coping responses relate to EBV–viral capsid antigen (VCA) antibody titers in healthy college students (Esterling et al. 1990), and because EBV-infected B cells may represent an important reservoir for HIV-1 (Rosenberg and Fauci 1991) and human herpesvirus–6 (HHV-6) may be an important cofactor for progression of HIV-1, we investigated the effects of the CBSM and exercise interventions on EBV and HHV-6 antibody titers in asymptomatic gay men (Esterling et al. 1992).

We found that HIV-1-seropositive men had higher EBV-VCA antibody titers than did HIV-1-seronegative men at every time point during the study. HIV-1-seropositive men who had been randomized to either CBSM or exercise interventions had significant

decreases in both EBV-VCA and HHV-6 antibody titers over the course of the intervention (indicating enhanced immunologic control of these latent viruses), compared with assessment-only control subjects, whose antibody titers remained constant over the 10-week period. HIV-1-seronegative men assigned to either intervention, compared with the control subjects, also showed decreased antibody titers and thus benefited from the intervention as well.

To further interpret these findings, we examined possible correlations between changes in anxiety and depression (as well as changes in CD4+ and CD8+ cell counts and in phytohemagglutinin-stimulated lymphocyte proliferation) and changes in antibody titers to EBV and HHV-6. However, no significant correlations were found; thus, we do not yet know the mechanism by which these changes occur. Interestingly, increases in anxiety and depression were significantly correlated with decreases in CD4 cell counts over the 10 weeks.

We also ruled out two alternative explanations for the change in EBV and HHV-6 antibody titers: the findings were independent of changes in nonspecific humoral measures (total IgG levels and possibly HIV-1-induced polyclonal B cell activation as measured by Forssman antibodies) and were not the result of recent infection with EBV (as measured by changes in antibody to the early antigen to EBV).

Finally, the 10-week aerobic exercise/training intervention resulted in significant increases in CD4 cell counts (of 220 cells/mm^3) in the HIV-1-seronegative men and a trend toward an increase (of 115 cells/mm^3) in the HIV-1-seropositive men that did not reach significance (LaPerriere et al. 1991). A subsequent study of the effects of exercise by our group (Perna et al. 1999) in a symptomatic, pre-AIDS group suggested the critical factor may be adherence. Adherent exercisers had a significant increase in CD4 count, whereas nonadherent exercisers demonstrated a decline.

Psychosocial Predictors of Follow-Up

Predictors of Distress at 5-Week and 1-Year Follow-Up

We examined whether coping strategies for dealing with HIV-1 antibody serostatus notification were related to distress levels re-

ported 5 weeks and 1 year later. Denial and disengagement coping strategies (3 weeks postnotification) were associated with greater depression both 5 weeks and 1 year after notification, whereas active coping, planning, and positive reinterpretation and growth coping strategies were related to lower depression scores. Importantly, we found that among asymptomatic HIV-1-seropositive homosexual men, lower perceived social provisions 5 weeks before antibody testing predicted less use of active coping and planning as coping strategies at 1 year follow-up (Antoni et al. 1991a; Friedman et al. 1991).

Psychosocial Predictors of Disease Progression at 2-Year Follow-Up

We also examined psychological predictors of disease progression to symptoms and to death at 2-year follow-up. Recall that at entry to the study the men did not know their HIV-1 serostatus and were all asymptomatic. At 2-year follow-up, 5 of the 23 men had developed AIDS, and 9 had developed symptoms (the 5 with AIDS plus 2 with thrush and 2 with oral hairy leukoplakia). For the 23 men who turned out to be HIV-1-seropositive, distress at diagnosis, HIV-1-specific denial coping (i.e., level 5 weeks postdiagnosis minus prediagnosis level), and low treatment adherence (attendance for both aerobic exercise/training and CBSM groups, frequency of relaxation practice and doing homework during the 10 weeks for those in the CBSM group) were all significant predictors of more rapid disease progression (Ironson et al. 1994a). Denial and low adherence remained significantly correlated with greater incidence of disease progression after control for CD4 number at entry to the study. We also found that changes in denial and in relaxation practice frequency were significantly correlated with immune status (CD4 cell counts, phytohemagglutinin proliferative response) 1 year later, and immune status at that time was significantly correlated with disease progression. Thus, this study demonstrated significant relationships between psychological variables on the one hand and both immune measures and disease progression on the other.

Another finding of this study was that the interventions per se

were not related to less morbidity or mortality at the 2-year follow-up. This finding, in combination with the finding of significant psychological predictors noted in the previous subsection of several variables that were intervention-related, suggests that being in an intervention is not enough; those who practice, attend regularly, and break through the denial, all of which can be accomplished during the intervention, are likely to benefit most.

Personality Correlates of Baseline Psychosocial Measures and Change During CBSM

Because our group CBSM requires subjects to interact with others and to be comfortable in disclosing very personal information concerning sexual behaviors and emotional responses to stressors, we were aware that certain personality variables might impede an individual's ability to benefit from the proposed intervention (Lutgendorf et al. 1992). Dispositional variables pertaining to hostility and cynicism measured on the Cook-Medley Hostility (Ho) Scale (Cook and Medley 1954) were found to be positively correlated with higher total mood disturbance (as measured with the POMS) and higher HIV-1-specific distress (as measured with the Impact of Events Scale [Horowitz et al. 1979) among the HIV-1-seropositive homosexual men previously studied. Hostility and cynicism were negatively correlated with total social provisions perceived and active coping strategies in this group. Across the 10-week CBSM period, higher cynicism scores predicted smaller decreases in POMS total scores and Impact of Events Scale avoidance scores in these men, and this suggests that difficulties related to the ability to trust others may have impeded the effectiveness of this group intervention. We also found that higher baseline repressive styles, as measured on the Compulsive scale of the Millon Behavioral Health Inventory (Millon 1982), predicted greater increases in denial coping over the 10-week CBSM period among HIV-1-seropositive homosexual men (Lutgendorf et al. 1992). Thus, dispositional variables associated with hostility, mistrust, and lack of emotional expression may impede the effectiveness of the proposed intervention.

Results of CBSM in Men With Symptoms

In our earlier studies, we found that CBSM can reduce distress and depression (and normalize immunologic status) among HIV-1-seropositive men during the stressful period immediately after notification of HIV-1 seropositivity and during the adjustment period after this notification. On the basis of these promising results, we wanted to know whether the CBSM intervention could help gay men adjust to the chronic burden of symptomatic HIV-1 infection. The 40 HIV-1-seropositive men enrolled in this study already knew their serostatus, had already experienced at least one HIV-1-related symptom (category B of the 1993 CDC staging definition), had not experienced an AIDS-defining illness (category C of the 1993 CDC staging definition), and had CD4 cell counts greater than 200 cells/mm^3 at entry to the study. The men were randomly assigned to the 10-week CBSM group or to a "usual care" control group.

The intervention group showed significant decreases in dysphoria, anxiety, and distress over the course of 10 weeks (Lutgendorf et al. 1997). Immunologically, there was a significant decrease in herpes simplex virus–2 (HSV-2) antibody titers in the intervention group, an indication of better control of this latent herpesvirus (Lutgendorf et al. 1997). Greater relaxation frequency was significantly associated with lower norepinephrine levels, with this association providing some support for decreased sympathetic nervous system activity as one possible mediator for intervention effects. The intervention also buffered decreases in dehydroepiandrosterone sulfate (DHEA-S) and increases in the cortisol/DHEA-S ratio (Cruess et al. 1999), suggesting another possible physiological mediator. Finally, evidence was found for changes in cognitive coping skills (e.g., acceptance) and social support as mediators of decreases in distress (Lutgendorf et al. 1998).

Summary

Taken together, the findings reported in this section suggest that behavioral interventions such as CBSM and aerobic exercise/train-

ing may reduce distress and depression (and normalize immunologic status) in HIV-1-seropositive men immediately after notification of HIV-1 seropositivity and during the ensuing adjustment period. Preliminary results for CBSM suggest that these findings may extend to HIV-1-seropositive men who are in the chronic phase of dealing with HIV-1-related symptoms. We have also identified several psychosocial factors that may predict disease progression. These effects may be mediated by increased use of active coping strategies (e.g., relaxation exercises, active coping, and planning), decreased use of denial/avoidance coping strategies, and increased social support perception and utilization.

Discussion

Behavioral Intervention Effects on Psychological Variables and Immune Function

We found that the CBSM intervention buffered the psychological and immunologic changes that accompanied the stressor of notification of HIV-1 seropositivity. Whereas untreated gay male subjects showed decrements in NK cell counts and small decreases in NK cell cytotoxicity from pre- to postnotification, HIV-1-seropositive men in the CBSM group showed no such decrements over a similar period. Over the subsequent 5-week period, the HIV-1-seropositive men in the CBSM group and those in the aerobic exercise training group showed significant decreases in previously elevated antibody titers to two herpesviruses, suggesting a normalization of some aspects of immune function (Esterling et al. 1992).

In addition to our own intervention studies with HIV-1-infected homosexual men (Antoni et al. 1991a, 1991b), two other relaxation intervention studies found similar results with healthy individuals (Kiecolt-Glaser et al. 1985, 1986), and studies with three other stress management protocols found intervention-associated immunologic changes in cancer patients (Fawzy et al. 1990b, 1993; Gruber et al. 1993) and in HIV-1-infected patients (Ironson et al. 1996). In con-

trast, a few studies reported negative results for the critical CD4 cell count measure in HIV-1-infected patients (Auerbach et al. 1992; Coates et al. 1989; Ironson et al. 1996; N. Mulder et al. 1995). (For a review of the impact of psychosocial intervention on immune function and health, see Ironson et al. 1995a.)

In one study of elderly individuals that compared progressive muscular relaxation training (three sessions a week for a month) with a no-intervention condition, the relaxation intervention was associated with significant increases in NK cell activity and decreases in HSV-2 antibody titers (both of which are consistent with improved immune function) (Kiecolt-Glaser et al. 1985). Another study by the same group of investigators found that frequency of relaxation practice in a group of medical students undergoing examinations was associated with higher helper T lymphocyte percentages (Kiecolt-Glaser et al. 1986), although the relaxation group overall did not differ from the control group in terms of impact on immune measures. Another study using a relaxation intervention (involving relaxation, guided imagery, and biofeedback training) found significant decreases in anxiety and significant increases in NK cell activity and lymphocyte proliferation responses among stage I breast cancer patients (Gruber et al. 1988, 1993).

A 6-week structured psychiatric group intervention incorporated relaxation as part of a stress management intervention for malignant melanoma patients that included health education, enhancement of problem-solving skills, and psychological support (Fawzy et al. 1990a). The intervention was associated with significant decreases in depression and total mood disturbance and increases in active behavioral and active cognitive coping. There were significant increases in large granular lymphocyte and NK cell percentages as well as in interferon-augmented NK cell cytotoxicity at 6-month follow-up, but only large granular lymphocyte percentage was significantly increased at the close of the 6-week intervention (Fawzy et al. 1990b). The subjects who showed increased NK cell cytotoxicity at the intervention baseline were less likely to experience recurrence 6 years later, but no association with survival time was found (Fawzy et al. 1993). Furthermore, the intervention subjects, compared with the control subjects, had

a significantly lower rate of death and a trend toward lower rates of recurrence (Fawzy et al. 1993). Survival time was also higher in an intervention group of metastatic breast cancer patients given weekly supportive group therapy sessions for a year compared with a usual-care control group (Spiegel et al. 1989). In fact, individuals in the intervention group survived, on average, nearly twice as long (36 months) as those in the control group. Since these researchers did not study immune measures, it is impossible to know whether these differences may have been the result of alterations in immunity; their current work, which includes immune measures, may shed some light on this question.

The study with negative results (Coates et al. 1989) compared a stress management intervention for HIV-1-seropositive men with a waiting-list control condition and found that the intervention had no impact on immune measures. Possible reasons for the discrepancy between this finding and the aforementioned positive findings from other studies include the following: 1) the Coates et al. (1989) study did not include many immune measures shown to be sensitive to psychosocial variables, such as NK cell cytotoxicity or herpes simplex virus antibody titers; 2) the group focus on AIDS-related issues may have been anxiety provoking (in fact, there was no evidence of affective changes in the intervention group, the reputed pathway by which immune changes occur); and 3) the study did not assess the frequency of relaxation practice, an issue whose importance was noted in the studies by Ironson et al. (1994) and Kiecolt-Glaser et al. (1985).

As noted, in addition to the Coates et al. study, three other studies found no impact on CD4+ cell numbers (Auerbach et al. 1992; Ironson et al. 1996; N. Mulder et al. 1995), a major disease progression marker for HIV-1 infection. However, findings from our study (Antoni et al. 1991a; Esterling et al. 1992; Lutgendorf et al. 1997) and the Ironson et al. (1996) study suggest that other immune measures relevant to health in HIV-1 infection, such as EBV, HHV-6, HSV-2, and NK cell cytotoxicity measures, may be favorably affected by a stress-reducing intervention.

In addition to the Fawzy et al. (1993) and Spiegel et al. (1989) findings showing main effects of a behavioral intervention on mor-

tality, both our study (Ironson et al. 1994) and one by Mulder et al. (1994) suggest that intervention-associated changes are related to follow-up immune and/or health measures. As noted in our study (Ironson et al. 1994), adherence (including attendance, frequency of relaxation practice, and doing homework), distress, and denial were related to disease progression over a 2-year period. (Denial and adherence remained as predictors after CD4 cell number at entry was controlled.) Changes in denial and relaxation frequency were also significantly correlated with immune status 1 year later. In the Mulder et al. (1994) study, 3 months of either CBSM or existential group therapy reduced distress levels, and these reductions in distress levels were predictive of the rate of CD4 cell count decline over a subsequent 2-year period.

We have also demonstrated that the proposed 10-week CBSM intervention can significantly lower both EBV and HHV-6 IgG antibody titers in asymptomatic HIV-1-seropositive homosexual men experiencing the acute stress of serostatus notification (Esterling et al. 1992). Although these decreases in EBV and HHV-6 antibody titers were not directly related to changes in distress levels, they were correlated with the increases in the use of active/involvement coping strategies and improvements in social provisions over the 10-week intervention period. In the 10-week study with symptomatic HIV-1-seropositive men, significant reductions in antibody titers to HSV-2 were found (Lutgendorf et al. 1997). Thus, CBSM might have an impact on, and even normalize, several measures of immunologic status in HIV-1-infected men.

Finally, as noted earlier, many studies showed a beneficial effect of behavioral interventions on the immune system, although this effect was not invariably shown. It is interesting to note that the negative studies did not measure several of the variables in which we found changes (i.e., EBV antibody titers, HHV-6, and HSV-2). Therefore, our results on immune function must be viewed tentatively and await replication. With this caveat in mind, we note that there is preliminary evidence, though not conclusive, that behavioral interventions can reduce distress and may affect both certain immune measures and disease progression, at least for certain subsets of participants. The results from our studies, and findings of

other studies, reported in this chapter suggest that the participants who benefit most are those who practice the most and are able to refrain from using maladaptive coping strategies.

Aerobic Exercise Training and Psychoneuroimmunology

Major immune findings for aerobic exercise/training included a significant decrease in antibody titers to EBV and HHV-6 and an increase in CD4 cells counts (significant for the HIV-1-seronegative individuals but only a trend for the HIV-1-seropositive individuals as a group) over the 10-week intervention. However, the adherent HIV-1-seropositive individuals did show a significant increase in CD4 cell count.

A review of exercise and psychoneuroimmunology (LaPerriere et al. 1994) noted three randomized studies examining the effects of exercise on psychological variables and immune function in HIV-1-seropositive subjects. Schlenzig and colleagues (1989) found reductions in anxiety and depression that were correlated with increases in CD4 cell counts at the end of the training period. Florijn (1992) found decreases in depression, fatigue, and anger in the exercise group. Furthermore, CD4+ and CD8+ cell counts were stabilized in the exercise group but showed a definite deterioration in the control group. In the third study, Rigsby and colleagues (1992) found a significant decrease in depression in the exercise group and a nonsignificant increase in CD4 cell counts (58 cells/mm^3). Taken together, these studies show a positive effect of exercise in reducing distress and in at least maintaining CD4 cell counts. Again, other studies have not included the immune measures that were most affected by our exercise intervention, and thus our findings await replication.

Importance of EBV, HHV-6, and HSV-2 in HIV-1 Infection

The importance of herpesvirus reactivation in HIV-1 infection, especially as it relates to psychosocial stressors, has been reviewed by Antoni and colleagues (1995). EBV reactivation has been shown to be associated with factors promoting HIV-1 replication and progression to AIDS (Carbonari et al. 1989; Hammarskjold and

Heimer 1988; Neri et al. 1991; Rosenberg and Fauci 1991). According to work from the laboratory of Gallo, co-infection with HHV-6 and HIV-1 may result in accelerated HIV-1 expression and cell death that may operate through direct activation of the HIV-1 long terminal repeat (LTR) (Lusso et al. 1989). This LTR contains several sites to which cellular or viral proteins can bind and trigger HIV-1 transcription (Lusso 1991). We found that even at the asymptomatic stage, HIV-1-seropositive men have significantly higher EBV and HHV-6 antibody titers than matched HIV-1-seronegative men (Esterling et al. 1992), and HIV-1 seropositive men have been shown by other researchers to display signs of EBV reactivation (Sumaya et al. 1986). Finally, HSV-2 may be a possible cofactor in the progression of HIV-1 infection. One study found that HSV-2 accelerated HIV-1 replication in co-infected CD4+ cells in vitro (Kucera et al. 1990). In addition, herpetic lesions due to HSV-2 may provide the entry way for HIV-1 into the body (Cannon et al. 1988).

Psychological Factors and Disease Progression

Several studies have prospectively examined the relationship between psychological factors (several of which are potentially modifiable through interventions), immune changes, and disease progression in HIV-1 infection. Methodologic issues of importance in rendering a sensitive test of the relationship between psychological factors and disease progression have been reviewed by Goodkin and colleagues (1994).

Coping

The relationship between coping, immune function, and disease progression has been examined, with predominantly positive results. As noted earlier, we found that the use of denial (and behavioral disengagement) to cope with notification of HIV-1 seropositivity was predictive of lower CD4 cell counts at 1-year follow-up (after control for CD4 cell counts at entry into study) and greater likelihood of progression to HIV-1-related symptoms and AIDS at 2-year follow-up (Ironson et al. 1994). Consistent with this

finding are the results of several other studies: Fawzy and colleagues (1993) found that active behavioral coping predicted survival 5 to 6 years later among malignant melanoma patients, and Solano and colleagues (1993) found that denial/repression was associated prospectively with the emergence of symptoms in a sample of HIV-1-seropositive individuals. Goodkin and colleagues found that use of active coping strategies predicted a lower number of physical symptoms 6 months prospectively (Blaney et al. 1992) and predicted higher CD4 cell count as many as 3.5 years prospectively (Goodkin et al. 1993). Similarly, C. L. Mulder and colleagues (1995a) found that active confrontational coping predicted decreased clinical progression over 1 year, and Blomkvist and colleagues (1994) found that active optimistic coping behavior was associated with prolonged survival in hemophiliac men. In contrast, Reed and colleagues (1994) found that "realistic acceptance" was a significant predictor of decreased survival time in gay men diagnosed with AIDS.

Although these findings of Reed et al. appear to contradict the findings from the previously cited studies, coping certainly seems to be an important variable to explore. One possible way of reconciling these findings is by hypothesizing that extreme levels of denial or of realistic acceptance might be dysfunctional. The notion that not dwelling on the negative aspects of HIV-1 infection might be beneficial was explored by C. L. Mulder and colleagues (1995b). They found that greater use of distraction predicted a slower rate of CD4 decline and less progression to immunologically defined AIDS over 7 years. Possible mechanisms for the role of denial suggested by Ironson and colleagues (1994) include a decrease in relevant self-care behaviors, preclusion of emotional expression, and interference with adaptive coping strategies.

Depression

A second variable explored in relation to immune function and disease progression, with conflicting results, is depression. Burack and colleagues (1993) found a faster decline in CD4 cell counts in depressed HIV-1-seropositive men, compared with their nondepressed

counterparts, for as long as 5.5 years. However, Lyketsos and associates (1993) found that depressive symptoms did not predict accelerated mortality or worse medical course over 8 years, although depressed HIV-1-seropositive men had lower CD4 cell counts and reported more AIDS-related symptoms. In addition, although Perry and colleagues (1992) found no association between a variety of psychological states and CD4 cell counts 6 months and 1 year later, they did find one variable related to depression, hopelessness, to be a significant predictor of CD4 cell count decline.

Similarly, Rabkin and associates (1991) found no association between depressive disorders, psychiatric distress, or stressful life events and HIV-1 illness stage or CD4 and CD8 lymphocyte subsets over a 6-month prospective period in a sample of gay men. They did, however, find that higher Hamilton Depression and Anxiety Rating Scale scores and Social Conflict Stressor scores significantly predicted the emergence of HIV-1-related symptoms during this period. This suggests that other aspects of immune status or other distress-induced changes might account for the correlations between symptoms and depression and distress. Moreover, Kemeny (1991) found that sustained depressed mood over a 2-year period was associated with a significantly greater likelihood of a steep rate of decline of CD4 cell counts. As noted earlier, in Mulder et al.'s (1994) study, reduction in distress levels after 3 months of either CBSM or existential group therapy was predictive of the rate of CD4 cell count decline over a subsequent 2-year period.

Finally, depression has been shown prospectively to be a predictor of mortality in several other diseases, such as cancer (Shekelle et al. 1981) and cardiovascular disease (Frasure-Smith et al. 1993), although the nature of the relationship between depression and overall cancer risk remains controversial (Fox 1989; Zonderman et al. 1989).

Fatalism

A third variable explored in the literature, by Kemeny and colleagues, is fatalism, or negative expectancies. In a series of three

studies, Kemeny (1994) found that men with a diagnosis of AIDS had a significantly shorter survival time and that fatalistic asymptomatic HIV-1-seropositive men were more likely to develop HIV-1-related symptoms over 2.5 to 3.5 years and to show a more rapid decline in CD4 cell counts. In addition, negative expectancies were found to interact with bereavement such that those with negative expectancies and multiple losses had the most marked declines in CD4 cell numbers.

Social Support

A fourth variable explored in relation to health in HIV-1 infection is social support. Solomon and Temoshok (1987) found that a rating of problem-solving help used by individuals with AIDS-related *Pneumocystis carinii* pneumonia distinguished between those who remained alive at follow-up and those who had died. Theorell and colleagues (1995) followed a cohort of HIV-1-infected hemophiliac individuals in Sweden and found that a group scoring low in availability of attachment had a significantly more rapid deterioration in CD4 cell counts, but not mortality, than those with high availability of attachment scores.

Finally, in reviewing the literature on long-term survivors of AIDS and integrating it with the findings from the longitudinal studies noted above, Ironson and colleagues (1995b) identified four factors related to longer survival with HIV-1/AIDS: healthy self-care, maintaining connectedness, having a meaning or purpose in life, and maintaining perspective. Preliminary empirical evidence for two of these factors—healthy self-care (collaborative relationship with one's physician) and life involvement—was found in a group of long survivors of AIDS in Miami (Ironson et al. 1998). Since the literature on long-term survival in HIV-1/AIDS is derived primarily from cross-sectional studies, and since a person's psychological state may change as a result of the disease, these factors should be viewed with appropriate caution until further study has been undertaken, including our own longitudinal study currently under way.

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Our research, combined with the rest of the literature, suggests that coping, affective state, expectancy, and social support are psychological variables of potential importance both for quality of life and for disease progression. There is some evidence, as well, that these factors can be modified by behavioral intervention.

Adherence, another variable suggested by our research findings, is related to psychological and immunologic intervention outcomes. Our findings support those of Kiecolt-Glaser et al. (1986), who demonstrated that individuals who more often practiced relaxation had a more positive immune change, suggesting that the degree to which one benefits from an intervention may be more important than simply being assigned to an intervention group. Finally, adherence may be related to a general personality dimension of conscientiousness—another variable that future studies may find useful to explore.

Conclusion

Our cognitive-behavioral stress management intervention 1) acts to buffer the distress (and immunologic changes) associated with learning of HIV-1 positive serostatus; 2) enhances or maintains adaptive coping strategies, such as social support seeking, planning for the future, and acceptance, during the weeks following diagnosis; 3) decreases maladaptive strategies such as denial and disengagement; 4) decreases social isolation following HIV-1 positive serostatus notification; and 5) has a normalizing effect on antibody titers to EBV and HHV-6 during the adjustment period after serostatus notification. In fact, we found that this intervention lowered IgG antibody titers to two herpesviruses in the cohort in our study. Findings from our longer-term, longitudinal observations of this cohort revealed that the use of maladaptive coping strategies (denial, behavioral disengagement) during adjustment to HIV-1-seropositive status notification predicted 1) greater depression 1 year later (involvement strategies predicted less depression);

2) lower CD4 cell counts and lymphocyte proliferative responses to PHA 1 year later; and 3) greater incidence of HIV-1-associated (non-AIDS) symptoms as well as frank AIDS 2 years later.

Aerobic exercise/training buffered the anxiety, depression, and immune changes associated with serostatus notification among those who were identified as having an HIV-1-positive serostatus. Furthermore, over 10 weeks, as with the findings for CBSM, there was a significant decrease in antibody titers to EBV and HHV-6, and this suggests improved immunologic control of latent herpesviruses. Finally, as with the CBSM group, adherence was associated prospectively with improved health at 2-year follow-up.

Our second CBSM effort targeted men who already knew of their HIV-1-positive serostatus but did not yet have symptoms. Again, we found significant decreases in maladaptive coping (mental disengagement, denial, and behavioral disengagement) and increases in active coping strategies (planning, coping, and acceptance).

Our third, and current, effort involves examining the efficacy of CBSM in men whose HIV-1 infection has already progressed to the early symptomatic stage. Preliminary findings for this population include a significant decrease in depression and HSV-2 antibody titers (an indication of improved immunologic control of these latent herpesviruses). Thus, CBSM may enhance or maintain adaptive (active involvement) coping strategies and perceptions of social support and decrease the use of maladaptive coping (denial and behavioral disengagement), with associated improved cellular immunologic control of some latent herpesviruses that are associated with disease progression.

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Chapter 10

Bereavement, Immunity, and the Impact of Bereavement Support Groups in HIV-1 Infection

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Bereavement, the loss of a beloved family member or close friend, is a major and often devastating life stressor that most people experience at least once over the course of a lifetime. Researchers have separated the process of bereavement into different stages (Clayton 1990; Raphael and Middleton 1987; Silverman 1966), but, overall, there is a consensus that within hours, days, or sometimes weeks of the loss, the bereaved experience considerable distress and a variety of decrements in psychosocial, immunologic, and physical well-being.

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Although people normally begin to resolve their loss within a few months, symptoms of distress and grief may persist for considerably longer or may be pathological from the beginning. So-called "pathological" or "atypical" grief has been distinguished from "normal" or "uncomplicated" grief by the former's chronicity, inhibition, delay, distortion, or severity (Zisook and DeVaul 1985). Prigerson and colleagues (1995) differentiate complicated grief from depressed mood in bereaved individuals; they demonstrated that a cluster of symptoms indicative of complicated grief was associated with longer-term functional impairment—a finding lending predictive validity and practical utility to this concept. Though there is no agreement concerning exactly where the boundary between normal and pathological grief should be drawn (Raphael and Middleton 1987), normal grief is generally recognized to be necessary for the process of bereavement to lead to recovery and resolution.

Bereavement and Psychological Distress

Lindemann (1944) was one of the earliest researchers to describe grieving and bereavement methodically, the attendant symptoms of psychological distress (depression and anxiety), and the potential for maladjustment. He was followed by many others in this endeavor (Garb et al. 1987; Harlow et al. 1991; Jacobs et al. 1987; Lesher and Bergey 1988; Norris and Murrell 1987; Rynearson 1987; Stroebe et al. 1993; Thompson et al. 1991; Zisook and Shuchter 1991; Zisook et al. 1987).

The bereaved experience more family stress (Norris and Murrell 1987), frequently use coping strategies associated with psychosocial dysfunction (Gass and Chang 1989), and experience inadequacies in resources such as social support (Oxman et al. 1992). Typical depressive symptoms following bereavement include crying, sleep disturbance, low mood, loss of appetite, fatigue, loss of interest, and poor memory. The majority of depressive symptoms after a loss are self-limiting and appear not to require professional attention (Bornstein et al. 1973; Breckenridge et al. 1986; Clayton 1990; Osterweis et al. 1984). However, depressive symptoms that persist during the first year after loss—a condition that occurs in

about 15% of widows or widowers (Clayton 1990), are indicative of pathological grief and generally require clinical intervention (Jacobs et al. 1987). Pathological grief also has been defined by the symptoms of separation distress, which include sighing, crying, yearning and searching for the deceased, and preoccupation with thoughts of the deceased (Kim and Jacobs 1991). Kim and Jacobs (1991) reported a significant association between pathological grief and major depressive disorder, as diagnosed by DSM-III-R criteria (American Psychiatric Association 1987). It should be pointed out that DSM-IV criteria for bereavement as a focus of clinical attention suggest that a bereavement reaction complicated by major depressive disorder may be diagnosed as early as 2 months after the loss (American Psychiatric Association 1994).

The presence of certain symptoms may differentiate a complicated bereavement reaction from normal grieving at any time after the loss:

- Guilt about things (other than action taken or not taken by the survivor at the time of death)
- Thoughts about death (other than the survivor's feeling that he or she should have died or would be better off dead)
- Morbid preoccupation with worthlessness
- Marked psychomotor retardation
- Prolonged and marked functional impairment
- Hallucinations (other than hearing the voice of or transiently seeing the deceased)

In a significant minority of cases, bereavement has been associated with more severe psychiatric sequelae, including depression with melancholic or psychotic features (Jacobs 1993; Rynearson 1990), as well as anxiety disorders such as posttraumatic stress disorder (PTSD), panic disorder, and generalized anxiety disorder (Jacobs et al. 1990). When the bereavement is unexpected or traumatic (e.g., accidental or combat deaths), the frequency and intensity of these sequelae are particularly high (Garb et al. 1987).

It is important to distinguish between grief and depressed mood as well as to differentiate both of these from clinical syndromes

such as major depressive disorder, particularly with respect to determining the impact of bereavement per se on immune function and physical health (as discussed later in this chapter). Grief is a specific measure of bereavement-related affect (Clayton 1982) and may be present and unresolved in the absence of complicated bereavement reactions (Neugebauer et al. 1992), depressed mood, and major depressive disorder. The severity of unresolved grief and acute mourning may be measured by instruments such as the Texas Inventory of Grief and its revision (Faschingbauer et al. 1977, 1987) as well as the Grief Experience Inventory and its revision (Lev et al. 1993; Sanders et al. 1979).

Increased cigarette smoking and the use of psychoactive substances such as alcohol, tranquilizers, and hypnotics also have been noted among spouses in the first year after bereavement (Clayton 1990; Zisook et al. 1987) and among bereaved homosexual men with human immunodeficiency virus–1 (HIV-1) infection or at risk for such infection (Martin 1988). In fact, a dose-response relationship was described for use of recreational substances (though excluding alcohol and marijuana) and abuse of prescribed sedative medications after a loss among bereaved HIV-1-infected individuals. Indeed, this increased substance use has been described as "the essence of morbidity of bereavement and the essence of the reaction to a stressful life event" (Clayton 1990). The use of sleeping pills or tranquilizers in the first month after a loss was found to be associated with difficulty in coping 2 years later (Lund et al. 1985).

The risk of any disturbance occurring after bereavement is higher in individuals who have a history of psychiatric disorders. For example, bereaved spouses with a history of major depressive disorder are more likely to manifest symptoms of anxiety and depression (Zisook et al. 1987), and those with a history of substance abuse or dependence are more likely to abuse the substances used in the past or other substances after bereavement (Clayton 1990).

Bereavement, Health Status, and Mortality

As previously noted, bereavement is associated with decrements in physical health (Kaprio et al. 1987; Lundin 1984; Parkes and

Weiss 1984). An increase in morbidity and mortality from a variety of illnesses was described in 40% of bereaved persons over the first 6 months after loss, with a 10-fold increase over the year following loss (Bloom et al. 1978; Verbrugge 1979). More recent research supports, though not invariably, an association of bereavement with mortality, with a relative risk of 2.1 for 7 to 12 months after a loss for men with few prior health problems; this risk remained greater than 1.0 for 2 years or longer (Schaefer et al. 1995). Much of this morbidity and mortality was due to cardiovascular disease; yet it has recently been hypothesized that myocardial infarction may also involve behavioral-neuroendocrine-immune interactions relating to cytomegalovirus, other herpesviruses, and *Chlamydia pneumoniae* infections (Goodkin and Appels 1997). Thus, a large proportion of increments in nonaccidental morbidity and mortality after bereavement may be related to decrements in immunocompetence.

Moreover, with bereavement, increases in sick days and more admissions to the hospital are characteristic of the year after loss (Parkes and Brown 1972). Evidence suggests that unresolved grief, which was reported in 18% in one cohort of homosexual men (Summers et al. 1995), may be ameliorated by intervention (Summers et al. 1991). Since bereavement may be related to decreased immunocompetence and to increased mortality among the physically healthy, the experience of bereavement itself, rather than complicated grief, may constitute sufficient rationale for clinical grief intervention to be offered proactively to an immunocompromised population (such as those infected by HIV-1).

Bereavement Within the Psychosocial Context of the Stressor-Support-Coping Model: Indications for Intervention

The group intervention used in our ongoing study with men, and piloted for HIV-1-positive women and women at risk for HIV-1 infection, aims to facilitate grief resolution and simultaneously modify the three predictors of psychological distress in our framework,

the Stressor-Support-Coping (SSC) model (see Chapter 6, this volume, for detailed discussion of this model): life stressors, social support, and coping strategy. The SSC model suggests that decreasing stressful life event exposure and impact, increasing social support availability and satisfaction, and improving use of adaptive coping strategies (active coping with controllable stressors and passive yet engaging coping strategies with uncontrollable stressors) decrease psychological distress. In turn, limbic-hypothalamic-pituitary-adrenal (LHPA) axis and sympathetic adrenomedullary system activation is decreased, and this buffers against decrements in cellular immune function, increments in viral load, and decrements in clinical health status.

As mentioned earlier, most bereaved individuals do not require a therapeutic intervention based on clinical need for support in order to deal with the grieving process itself. There is great diversity in coping with loss (Shuchter and Zisook 1990); for example, many people grieve quietly without painful sequelae (Wortman and Silver 1989). Still, much of what is now considered normative grief is nonetheless painful or dysfunctional. Nearly half of patients with uncomplicated bereavement meet the diagnostic criteria for a depressive disorder during the first year after loss, and depressive symptoms may recruit or intensify grief symptoms. Women are known to have higher levels of grief than men, especially during the first year after loss, and to seek support more often (Parkes 1990); however, some research suggests that bereavement-related health decrements may be less prominent in women, since women typically have broader, more diversified social support networks than do men (Helsing and Szklo 1981). Such a rationale may apply, at least, to those without chronic or immunosuppressive illness at the time of their loss.

Since pathological distress appears to occur less frequently in HIV-related bereavement as the epidemic has progressed (Neugebauer et al. 1992), our bereavement support group intervention is intended primarily for those experiencing bereavement but remaining in the normal range of psychological function. As mentioned earlier, we piloted the intervention used for HIV-1-seropositive and "at risk" homosexual men and modified it for

HIV-1-seropositive and at-risk women (Goodkin et al. 1995a). Though the topics provided are nearly identical to those used in the intervention for men, the process has been adapted to further stimulate group and therapist mutuality, equality, and authenticity regarding HIV prevention intervention in women (Levine et al. 1993) in order to facilitate individualized grieving.

Social support, as indicated earlier, is greatly decreased after bereavement and may mediate associated immunologic (Baron et al. 1990) and health effects (Parkes 1990) and be related to long-term survivorship in AIDS (Remien et al. 1992). A high level of social support is the single most consistent predictor of better psychological adjustment postbereavement, an effect observed in homosexual men (Lennon et al. 1990). Active coping style (e.g., assertiveness with medical care providers) has been shown to be positively related to long-term survivorship as well (Solomon et al. 1993). Bereavement support groups have been shown to reduce distress, specifically among HIV-1-seropositive individuals, as demonstrated in our ongoing study (Goodkin et al. 1994a) and in others (McCallum et al. 1989; Sikkema et al. 1995). Other studies have focused on bereavement and immune function in HIV-1 infection (Kemeny et al. 1994). However, our ongoing study of a group intervention for bereavement in HIV-1-infected and at-risk homosexual men is, to our knowledge, the first to investigate simultaneously both a bereavement support group intervention and immune effects in HIV-1 infection.

Issues in Bereavement Specific to HIV-1 Infection

Bereavement, defined as the loss of a lover or a close friend, is especially common in homosexual men because of the toll that AIDS has exacted on this group in the United States (Klein 1994; Klein and Fletcher 1986; Martin 1988; Martin and Dean 1993; Neugebauer et al. 1992). Specific issues for bereaved homosexual men involve the following areas:

- Isolation
- Discrimination

- Homophobia
- Lack of family support
- Exacerbated uncertainty about the future
- Lack of a tradition for mourning or of a descriptive title for mourners
- Forced sexual preference disclosure
- Lack of recognition for financial benefits and for the right to be involved with medical care and funeral plans
- More discussion of sexuality and greater fear of resuming sexual activity
- Greater expectations from opportunities for new attachments, and greater complications in reentry and resocialization

As early as 1985, the incidence of AIDS-related bereavement was reported to be 27% in a sample of 746 homosexual men in New York (Martin 1988). Over a 2-year follow-up, 44% of the men had lost a close friend or lover, and another 5% reported having experienced at least one loss over three or more consecutive years. There was a direct association between the number of bereavements and various signs and symptoms of distress (e.g., traumatic stress, demoralization, insomnia, sedative use and use of other recreational substances, and use of psychological services for AIDS-related concerns). Psychological distress was highest among men who were themselves infected with HIV-1, and distress increased directly with the number of bereavements—a finding which suggests that the effect of multiple bereavements was cumulative over 5 years. However, over 7 years homosexual men eventually reported fewer and briefer symptoms of psychological distress associated with bereavement due to AIDS—a finding which suggests that these men were becoming habituated to loss—though the subjective sense of threat remained elevated (Martin and Dean 1993).

Neugebauer and colleagues (1992) interviewed 207 homosexual men in New York City and found that 51% of the respondents had lost a close friend or lover to AIDS since the beginning of the epidemic. Nearly one-fifth of the subjects had lost three or more

friends or lovers, and about as many had experienced at least one of these losses in the 6 months before the interview. More severe bereavement reactions, such as extreme levels of preoccupation with the deceased, were more common in subjects with multiple losses. However, there were no correlations between the number of AIDS-related losses and the overall level of depressive symptoms or the presence of syndromal depression (though there were correlations between the number of AIDS-related losses and grief level). The lower frequency of complicated grief reactions was interpreted by Neugebauer et al. as representing the acceptance of death in the age of HIV/AIDS and greater mobilization of the homosexual community—that is, death had come to be "less of an event than an environment."

An alternative explanation for the decreased frequency of complicated grief reactions is that multiple loss reactions more closely resemble PTSD (as described by Horowitz et al. [1980] for a single loss) than a depressive syndrome. This interpretation would fit with the descriptions given of a less overt reaction, in that PTSD-like responses would constitute numbing to losses and avoidance of stimuli related to loss. S. J. Klein (1994) coined the term "multiple loss syndrome" to describe a frequent clinical picture in which homosexual men with multiple losses of significant others to AIDS present with symptoms not unlike those of an acute response to disaster. However, natural disasters, such as Hurricane Andrew (an event experienced by the individuals in our cohort), are followed by broad community support; moreover, they are of finite duration (typically quite brief, though severe). Multiple loss syndrome is especially prominent when the total loss burden history is characterized by insufficient time to anticipate the next loss and grieve the prior loss, resulting in a numbing due to "overload" (described as "bereavement burnout"), social withdrawal, isolation, loneliness, and a sense of lack of control.

In our prior longitudinal, natural history study (described in Chapter 6, this volume), we found that 50% of the sample experienced bereavement during the course of the study, with half of this group experiencing the loss of at least one close friend or lover. Bereavement, then, may be considered a chronic stressor for homo-

sexual men from two points of view: chronicity (lasting for 2–4 years) (Zisook et al. 1987) and multiplicity (Martin 1988; Martin and Dean 1993; Neugebauer et al. 1992). Some of these bereavements may be sudden and traumatic; such losses have been associated with more severe psychiatric sequelae (Garb et al. 1987; Rynearson and McCreery 1993), a finding suggestive of a synergism between trauma and loss.

In contrast to the findings from the studies by Neugebauer et al. (1992) and Martin and Dean (1993), our current data on multiple loss from our ongoing bereavement support group study for HIV-1-seropositive and at-risk homosexual men show a significant relationship between total number of losses due to AIDS experienced and overall level of distress (as assessed with the Profile of Mood States [POMS; McNair et al. 1971] and other distress measures), clinically rated ($P = 0.04$) (but not self-reported) depression (as assessed with the Hamilton Rating Scale for Depression [Williams 1988]), and anxiety ($P = 0.09$) (as assessed with the Hamilton Anxiety Rating Scale [Williams 1988]). Importantly, multiple loss also was significantly and positively related to greater dysfunction in daily life activities (both psychosocial activities) ($P = 0.04$) and, though less so, to overall activities (psychosocial and physical combined) ($P = 0.07$). These findings suggest that the differences observed between the New York studies (Martin and Dean 1993; Neugebauer et al. 1992) and our Miami study may be related to a broader and longer impact of the epidemic in New York (still by far the U.S. city with the highest total number of AIDS deaths since the epidemic began) than in Miami, despite the fact that Miami is a major AIDS epicenter. Perhaps, the relation of multiple loss to clinically rated but not self-reported depressed mood in our sample can be attributed to denial or numbing (described in multiple loss syndrome) in response to presentation with a self-report mood measure.

The characteristics of the effects of multiple loss and other special characteristics of the HIV disease process—including the relative youth of those affected by the disease, the heterogeneity of symptoms and diseases present (before and after the diagnosis of AIDS), the variable time course of progression, the loss of one's

child (in mothers infected with HIV-1), and the socioeconomic and cultural characteristics of populations currently most affected by HIV-1—suggest that caution must be exercised in generalizing the results of earlier, non-HIV-1-associated conjugal bereavement studies to studies of bereavement in HIV-1-infected or at-risk homosexual or bisexual men and women.

For HIV-1-seropositive individuals, bereavement acts as a stimulus for additional distress concerning mortality (Martin and Dean 1993; Martin et al. 1989). In one study, 65% of the subjects referred for bereavement counseling linked bereavement to their own mortality (Sherr et al. 1992). In another study, individuals who had recently lost a partner and who had AIDS-related symptoms were significantly more likely to report suicidal ideation (Schneider et al. 1991). On the other hand, the bereaved can express heightened existential awareness that is associated with positive psychological changes (Yalom and Lieberman 1991), although it is not yet clear to what extent this has occurred in those experiencing AIDS-related bereavements.

The importance of material and emotional social support in AIDS-related bereavement was shown by Lennon and colleagues (1990). Therein, the grief scores for men who received inadequate social support were higher than those for men who received adequate support. This was predicted by our SSC model, in which unavailable, unsatisfactory, or insufficient social support augments the impact of life stressors (Goodkin 1990; Goodkin et al. 1993a, 1993b, 1993c).

Although a strong positive correlation between bereavement and the use of sedatives or other recreational drugs has been reported, in one study bereavement did not appear to be correlated with problems due to drinking and substance use (Martin 1988). Still, alcohol use is associated with decrements in natural killer (NK) cell cytotoxicity when controlling for the presence of major depressive disorder (Irwin et al. 1990), and we found that alcohol use in the normal range was associated with lower levels of this immune function as well (Goodkin et al. 1992a). Use of other substances, such as cocaine (Klein et al. 1988), marijuana (Friedman et al. 1988), benzodiazepines (Descotes et al. 1982), opioids (Donahoe

and Falek 1988), and nitrite inhalants (Haverkos 1988), is associated with decrements in other immune measures in vitro (e.g., lymphocyte proliferation in response to mitogens, and interferon-γ production). Alcohol use– and substance use–associated decrements in functional and phenotypic immunologic measures in addition to those associated with bereavement are of special concern to HIV-1-infected individuals, who may be already severely immunocompromised; however, the clinical implications of such recreational substance use for disease progression remain to be clearly demonstrated.

Treatment Issues in Bereavement

Treatment varies for bereaved individuals with depressive manifestations or other complications. For the elderly population, Gilewski and colleagues (1991) offer two alternatives. The first is a minimalistic intervention that essentially allows the bereaved to work through their grief at their own rate without labeling lengthy, or otherwise difficult, grieving as abnormal. The second, more aggressive professional alternative is to respond to bereavement in the same manner as to clinical depression—that is, with antidepressant medication or with behavioral, cognitive, or psychodynamic therapy.

With the population of HIV-1-infected individuals or individuals at risk for HIV-1 infection, the issues are again somewhat different than they are for the elderly. Bereavement has been associated with decrements in both phenotypic and functional immune measures (Goodkin et al. 1993, 1994b, 1995b, 1996). Since the healthy elderly (despite immunosenescence) may be better able to buffer these decrements than immunocompromised individuals, therapeutic intervention may be more strongly indicated for those who already are immunocompromised. Jacobs and colleagues (1987) showed that 7 of 10 spouses demonstrated moderate to marked improvement in depressive symptoms during a 4-week trial of tricyclic antidepressants. However, some antidepressants (e.g., amitriptyline) may suppress T cell proliferative

responses to mitogens (Audus and Gordon 1985; Surman 1993) and promote malignant tumor development (Brandes et al. 1992), especially at high doses (Miller 1987), although such immunologic effects have not been confirmed by clinical studies of the HIV-1-infected population to date (Rabkin et al. 1994). Moreover, fluoxetine was actually shown to be associated with an increase in NK cell cytotoxicity (Klimas et al. 1993). Possible immunopharmacologic side effects of psychotropic agents—both toxic and salutary—are of particular relevance and concern to bereaved HIV-1-infected individuals, as well as to the HIV-1-infected population in general.

Regarding immunologic effects of behavioral interventions, one study of terminal cancer patients showed enhanced immune system function when patients used mental imagery and received relaxation training (Gruber et al. 1987). Other studies of relaxation training have shown that this technique decreases psychological distress and is associated with increments in selected immune measures (Houldin et al. 1993; Kiecolt-Glaser et al. 1985). In HIV-1-seropositive individuals, aerobic exercise training was associated with salutary immunologic effects—a buffer against a decrement in NK cell count and an increase in CD4 cell count (specifically, the "naive," suppressor-inducer subset) (LaPerriere et al. 1990, 1991). Cognitive-behavioral stress management has also been shown to have salutary immunologic effects in HIV-1-positive individuals, with increments in CD4 and NK cell count as well as, to a lesser extent, lymphocyte proliferation in response to phytohemagglutinin (Antoni et al. 1991). However, a high level of social support is the single most consistent predictor of better psychological adjustment after bereavement (Gass 1987; Windholz et al. 1985), and bereavement support groups have been shown to reduce distress in non-HIV-infected individuals (Kay and Portillo 1989; Marmar et al. 1988) as well as in HIV-1-infected individuals (Goodkin et al. 1994a; McCallum et al. 1989). Hence, bereavement support group techniques constitute the appropriate primary clinical approach to the bereaved and are therefore of greatest interest in terms of their corresponding potential psychoneuroimmunologic effects in this population.

Bereavement Support Group Intervention for Individuals With HIV-1 Infection

Intervention Design

The design of the bereavement support group intervention in our study derives from three areas of prior work. One is the research of Spiegel and colleagues (1981, 1989), who showed that a support group intervention for terminal breast cancer patients increased survival time by a factor of nearly two. A second influence is the framework for bereavement groups offered by Yalom and Vinogradov (1988) that emphasizes self-disclosure, sharing mutual fears and concerns, and working through feelings about death. The third element is the SSC model outlined earlier that incorporates life stressors, social support, and coping style as major determinants of grief level and psychological distress in general (Goodkin 1990; Goodkin et al. 1993a, 1993b, 1993c).

Consequently, an aim of our intervention is to modify these three predictors of the SSC model—life stressors, social support, and coping style—through a bereavement-focused supportive group process. The intervention emphasizes the importance of maximizing social support to buffer the negative impact of bereavement and to reduce loneliness. Stressor management is also emphasized in that the participant is encouraged to actively monitor stressor burden and accurately appraise the controllable aspects of attendant stressors. A cognitively oriented aspect of the intervention promotes increasing use of strategies for active coping with controllable stressors associated with bereavement, while emphasizing an adaptive, emotion-focused form of passive coping—emotional expression and spirituality—with the loss itself. The goal of the group is to confront and resolve the existential crisis posed by bereavement in the context of HIV-1 infection by enhancing the process of working through grief as well as by improving coping adaptation, social support utilization, and the stressor management skills that participants bring to bear on the multiple stressors in their lives.

The intervention design consists of a standardized, semistructured protocol with 10 specific session topics used in repeating cycles. These topics are structured to help participants resolve bereavement-related issues while simultaneously intervening on the three domains of the underlying SSC model (life stressor appraisal, social support utilization, and coping strategy selection). Rather than constituting a rigid focus, the topics serve as springboards from which the feelings and needs that the participants bring to each group session are given shape and direction. The topics comprise three clusters, reflecting the process of grief work (Table 10–1). The first cluster—*making contact*—consists of discussion of what bereavement is, the bereaved's relationship with care providers and the medical community, and the disposition of the loved one's belongings and the economic impact of bereavement. The second cluster—*emotional expression/ventilation*—consists of four topics: interactions with the family of the deceased; past relevant death experiences and level of homosexual community loss; survivor guilt and relief; and implications for one's own mortality. The third cluster—*moving on, resolution, and consolidation*—consists of management of distressing feelings, recruitment of social support, and discussion of what direction the bereaved can take after bereavement and what he or she can gain from the experience. This threefold template—making contact, emotional expression, and moving on—provides the structure for the topics and constitutes a process orientation for conducting each session.

Groups meet weekly, with each session lasting 90 minutes. Participants may join at any point in the 10-session cycle. The groups are led by two cotherapists with experience both in treating individuals with HIV-1 infection and in conducting groups for individuals who are bereaved or have a terminal illness. HIV-1-seropositive and HIV-1-seronegative participants attend separate groups because of differences in issues regarding confidentiality and perceptions of their own mortality. Unlike most traditional psychotherapy groups, outside contact between participants is encouraged so that participants can build their social support network, and psychodynamically oriented interventions involving interpretations of any participant's past are not offered. Because the groups are

Table 10–1. Bereavement support group intervention for individuals with HIV-1 infection

Making contact
Discussion of what bereavement is
Bereaved's relationship with care providers and the medical community
Disposition of the loved one's belongings and the economic impact of bereavement
Emotional expression/ventilation
Interactions with the family of the deceased
Past relevant death experiences and level of homosexual community loss
Survivor guilt and relief
Implications for one's own mortality
Moving on, resolution, and consolidation
Management of distressing feelings
Recruitment of social support
Discussion of what direction the bereaved can take after bereavement and what he or she can gain from the experience

conducted as part of a research study, therapist contact with participants outside the group is limited and monitored to ensure that any outcome effects observed are the result of the group therapy intervention and not to extraneous sources of therapist support. For similar reasons, participant contact with other providers and services is monitored. Participants are entitled to, on request, a total of 90 minutes of individual contact with the group therapists beyond the group sessions and the exit interview at the end of the 10 sessions. All such contacts are recorded on a log sheet. For service providers outside the study, participants are asked to indicate, for the month prior to their assessment, the quantity, regularity, and usefulness of contacts in the following areas: medical care, associated health care (e.g., dietitian), counseling (individual or group), nontraditional therapy, AIDS/HIV support groups or programs, alcohol/drug support groups, other groups (e.g., relaxation, psychoeducational), spiritual support, and social services.

Psychoneuroimmunology of Bereavement in HIV-1 Infection

In an earlier study (see Chapter 6, this volume), we found that our theory-driven SSC model was associated with changes in both psychological (distress) and immune outcome measures in asymptomatic HIV-1-seropositive homosexual men. The SSC model was simultaneously tested on two groups: asymptomatic HIV-1-seropositive homosexual men (CDC stage A, formerly CDC stages II and III; $n = 84$) and HIV-1-seronegative "at risk" control subjects ($n = 44$). Immune measures chosen were both phenotypic (absolute count and percentage of CD4+ T lymphocytes, and CD4/CD8 ratios) and functional (NK cell cytotoxicity and proliferative response to the T cell mitogen phytohemagglutinin at a concentration of 10 μg/mL). Macronutrient and micronutrient nutritional status, cigarette smoking, prescribed medication use, and current and past use of alcohol and recreational substances were included as control measures.

One component of the SSC model, life stressor count, was negatively associated with CD4 cell count and lymphocyte proliferation in response to phytohemagglutinin—a function of T lymphocytes. Another component, social support, showed a positive, direct association with lymphocyte proliferation in response to phytohemagglutinin. There was also a trend for social support to buffer the negative impact of life stressors on NK cell cytotoxicity (Goodkin et al. 1992a). A final component, coping strategy, showed the hypothesized positive association between active coping and NK cell cytotoxicity. Similarly, passive, maladaptive coping—measured by disengagement and denial—showed the hypothesized negative association with NK cell cytotoxicity. These results indicate that all three components of the SSC model accounted for variance in immune measures in the HIV-1-infected individuals. Further, changes in the CD4 cell count were significant for both HIV-1-seropositive and HIV-1-seronegative subjects, with the relationship being greater in seronegative subjects. Relationships between psychosocial and immune measures were consistently stronger in HIV-1-seronegative than in HIV-1-seropositive subjects. Although these results suggest a "muting" process, this term typically ap-

plies to dampening of a normal, physiological response, which cannot yet be considered conclusively demonstrated across the results from this study.

The power of our SSC model as tested in this earlier study was limited by the longitudinal natural history design employed. In particular, the life stressor measure allowed for a variety of life stressors, with a range of intensities, occurring at different time intervals before the assessments of psychosocial and immune measures. This may have accounted for the need for a large group of control variables to demonstrate psychoneuroimmunologic relationships. Therefore, in subsequent research, we chose to study bereavement—a specific, frequent, and highly powerful life stressor in our study population—in an attempt to reduce the variation associated with the analysis of a composite measure of life stressors of different types and intensities.

In this subsequent study of bereaved subjects, all initial assessments occurred within 6 months of the loss of a close friend or lover. Participants underwent a second assessment 6 months later. The occurrence of bereavement was associated with hypothesized decrements in NK cell cytotoxicity and another functional immune measure, the proliferative response of lymphocytes to phytohemagglutinin, replicating the results of prior research in conjugal bereavement. In addition, the bereaved sample showed decrements in the absolute count of CD4+ T lymphocytes ($n = 63$; $P = 0.03$) and the CD4 percentage ($n = 61$; $P = 0.006$), in addition to the CD4/CD8 ratio ($n = 63$; $P = 0.01$).

The simultaneous analysis of life stressors, social support, and coping style conducted on bereaved and nonbereaved asymptomatic HIV-1-seropositive homosexual men demonstrated decrements in NK cell cytotoxicity at two separate time points—within 6 months of to as long as 1 year after a loss (Goodkin et al. 1996)—extending earlier work on the time course of NK cell cytotoxicity decrements after the loss of a spouse. We have also described increments in NK cell cytotoxicity associated with active coping style within and outside the context of bereavement, again controlling for nutrition, prescribed medications, and alcohol and substance use (Goodkin et al. 1992a, 1996).

Previous studies of both conjugal bereavement (Irwin et al. 1988; Linn et al. 1984) and bereavement in HIV-1-infected homosexual men (Kemeny et al. 1994) suggested that depressed mood mediated the associated immunologic decrements observed. In our study, however, in which there was control for overall psychological distress as well as depressed mood in our theory-driven SSC model, we did not observe any changes in the results regarding the predictive power of the occurrence of the loss itself. Interestingly, differential immune associations were found as a function of time interval after the loss, with NK cell cytotoxicity decreasing at the first assessment (without a change in the proliferative response to phytohemagglutinin), and the response to phytohemagglutinin decreasing at the second assessment (when NK cell cytotoxicity had started to return to baseline, though it was still significantly suppressed) (Goodkin et al. 1996). This pattern suggests that these decrements may be mediated by different mechanisms. The sympathetic adrenomedullary system may play a primary role in the decrements in NK cell cytotoxicity observed at the first assessment, while the LHPA axis may play the primary role in the later decrements observed in lymphocyte proliferative response to phytohemagglutinin. Further analysis of these data revealed that active coping style was more positively associated with NK cell cytotoxicity in bereaved HIV-1-seropositive homosexual men than in the nonbereaved in our earlier study. Background life stressor count, outside of bereavement itself, remained negatively associated with lymphocyte proliferation to phytohemagglutinin in the SSC model, a confirmation of an additional association specific to bereavement on this measure. In addition, social support at the first assessment after a loss predicted NK cell cytotoxicity 6 months later for bereaved HIV-1-seropositive men ($P = 0.02$) but not for the nonbereaved.

Regarding the immunologic results of the intervention, 119 homosexual men (74 HIV-1-seropositive and 45 HIV-1-seronegative) were randomized to our bereavement support group intervention (HIV-1-seropositive = 51; HIV-1-seronegative = 29) or to a community comparison standard-of-care control condition (HIV-1-seropositive = 23; HIV-1-seronegative = 16). Psychological distress

measures and a phenotypic panel for CD4 and NK (CD56+CD3–) cell counts from peripheral venous blood were obtained preintervention, postintervention, and at 6-month follow-up.

For both HIV-1-seropositive and HIV-1-seronegative men, psychological distress ($P = 0.004$) and grief ($P = 0.04$) were significantly reduced after the intervention in a yet larger cohort ($N = 166$) (Goodkin et al. 1999b). There was a statistically significant buffering against a decrement in CD4 cell count over 6 months (Goodkin et al. 1998). In the HIV-1-seropositive group the CD4 cell count was maintained ($\text{mean}_{T1} = 351$ cells/mm^3; $\text{mean}_{T3} = 329$ cells/mm^3), whereas in the HIV-1-seropositive control group the CD4 cell count decreased ($\text{mean}_{T1} = 433$ cells/mm^3; $\text{mean}_{T3} = 372$ cells/mm^3) ($P = 0.04$) (Figure 10–1). In the group of HIV-1-seronegative men, there was an increase in CD4 cell count, from a mean at T1 of 821 cells/mm^3 to a mean at T3 of 933 cells/mm^3 in intervention subjects and a decrease from 800 cells/mm^3 at T1 to 712 cells/mm^3 at T3 in control subjects. Similarly, in another subsample ($N = 56$) of HIV-1-seropositive men, there was an increase in NK cell count between pre- and postintervention assessment ($n = 36$) relative to the control group ($n = 20$) ($\text{mean}_{T1} = 79.5$ cells/mm^3; $\text{mean}_{T2} = 101.5$ cells/mm^3) ($t = 2.5$, $P \leq 0.02$). Hence, it might be concluded that our bereavement support group intervention was associated with significant improvement in both psychological and immunologic (CD4 and NK cell count) status. In addition, there was a statistically significant reduction in plasma cortisol level in both the HIV-1-seropositive and -seronegative intervention subjects with respect to their controls over 6 months ($N = 119$) (Goodkin et al. 1998) (Figure 10–1). Further, the change in CD4 cell count was significantly associated with the change in plasma cortisol level, suggesting that the intervention-induced reduction in plasma cortisol level mediated the salutary immunologic effect we observed on the CD4 cell count. Moreover, health care visit use was significantly reduced over 6 months by this intervention as well for both HIV-1-seropositive and -seronegative subjects ($P = 0.023$) (Goodkin et al. 1998). This suggests that the immunologic effect observed translated into a clinical health benefit. In addition, it suggested that the clinical health benefit might

generalize to anyone who suffers a loss within 6 months, as this effect was observed in physically healthy, HIV-1-seronegative individuals. Finally we recently reported that a significant buffer against an increase in plasma viral load was observed with the intervention (at T1 and T2) ($N = 36$), after control for antiretroviral medication usage, prophylaxis against lethal complications of HIV-1 infection, baseline viral load, baseline CD4 cell count, and Centers for Disease Control and Prevention–defined stage of clinical disease progression ($P = 0.001$) (Goodkin et al. 1999a). The magnitude of the effect was a relative mean change of 0.78 $\log_{10}$ in plasma HIV-1 RNA copy number between conditions—greater than the change of 0.50 $\log_{10}$ required to document the effect of antiretroviral medications.

Our bereavement support group intervention has demonstrated a buffer against a decrement in CD4 cell count and against an increment in plasma viral burden. The effect on CD4 cell count was related to a reduction in plasma cortisol. The intervention, therefore, indicated a pathway from distress and grief reduction to clinical health benefit (on health care visit use). On the basis of the preliminary neuroendocrinologic, immunologic, virologic, and clinical health visit use results of our support group intervention, we expect that this intervention will be associated with decreased clinical progression to 1993 CDC stage C (i.e., clinically defined AIDS) in bereaved HIV-1-seropositive homosexual men. Also, intervention-mediated increased frequency of positively rated life events, increased social support utilization, and increased use of active coping strategies are predicted to be associated with immunologic enhancement in cell count and function, as well as decreased clinical progression, in HIV-1-seropositive homosexual men and with improved general physical health status and decreased frequency of illness in HIV-1-seronegative homosexual men.

Preliminary results reported from our bereavement support group pilot intervention study for HIV-1-positive and at-risk women suggest that a similar study should be performed in these populations. Although results of the bereavement support group intervention appear to be well demonstrated for a single, recent loss, it may be necessary to develop other interventions specific to

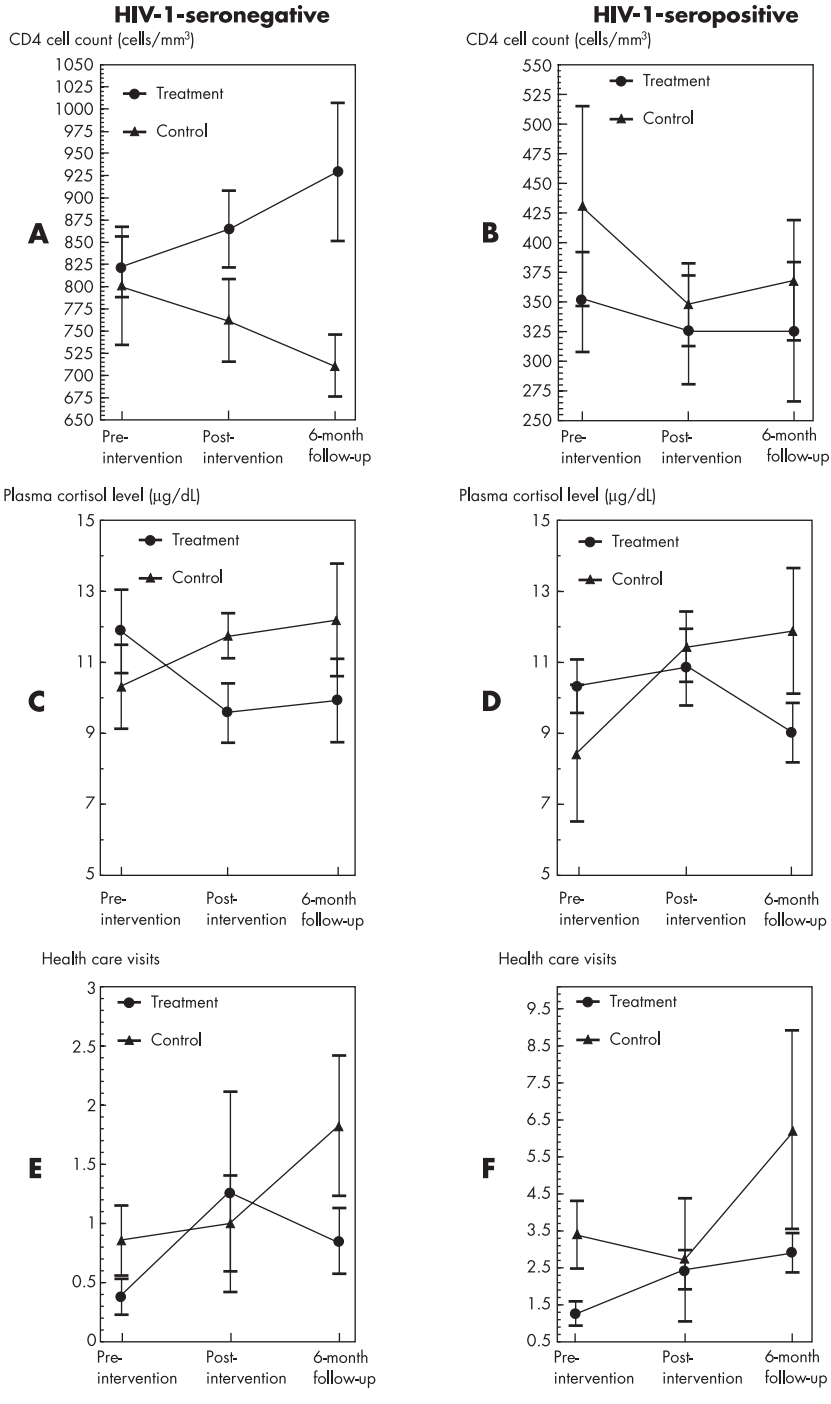
HIV-1-seronegative
HIV-1-seropositive
CD4 cell count (cells/mm3)
Treatment
Control
A
B
Pre-intervention
Post-intervention
6-month follow-up
Plasma cortisol level (µg/dL)
C
D
Health care visits
E
F

Figure 10–1. CD4 cell count, plasma cortisol level, and health care utilization change in HIV-1-seropositive and HIV-1-seronegative individuals. **(A and B)** Regarding the CD4 cell count outcome, among HIV-1-seronegative intervention subjects (A) the mean CD4 cell count increased progressively, whereas for HIV-1-seronegative control subjects there was a progressive decrease. For HIV-1-seropositive subjects (B) the mean CD4 cell count was higher at baseline (statistically controlled herein) among control subjects than among their intervention counterparts. However, the change in CD4 cell count reflected a decrease overall among control subjects, whereas for HIV-1-seropositive intervention subjects the CD4 cell count remained stable. **(C and D)** Regarding plasma cortisol level, among HIV-1-seropositive intervention subjects (D) mean plasma cortisol level stabilized initially postintervention and then decreased, as assessed at 6 months, while the mean plasma cortisol level of HIV-1-seropositive control subjects increased at T2 and again, though less substantially, at 6 months. In HIV-1-seronegative intervention subjects (C), unlike their HIV-1-seropositive counterparts, mean plasma cortisol levels initially decreased postintervention, a change that was essentially maintained at 6 months. The HIV-1-seronegative control subjects showed a pattern similar to that seen in their HIV-1-seropositive counterparts, with an increase in the mean at T2 and again, though less substantially, at T3. **(E and F)** Regarding the clinical outcome on health care visit utilization, among HIV-1-seropositive control subjects (F) mean health care visit utilization increased, whereas for HIV-1-seropositive intervention subjects there was a smaller, progressive increment. Among HIV-1-seronegative subjects (E) a similar pattern of change in the mean number of health care visits was observed. For all panels, standard errors are shown by vertical bars.
Source. Reprinted from Goodkin K, Feaster DJ, Asthana D, et al.: "A Bereavement Support Group Intervention Is Longitudinally Associated With Salutary Effects on the CD4 Cell Count and Number of Physician Visits." *Clinical and Diagnostic Laboratory Immunology* 5:382–391, 1998.

the traumatic aspects of the associated psychological distress related to the experience of multiple losses due to AIDS. Such an approach would provide optimal support of psychological and, potentially, associated immunologic and physical health status in the face of the onslaught of this epidemic.

In sum, these findings suggest that a supportive bereavement group intervention might be effective in enhancing immune function, decreasing viral load, and—as a possible outcome—deterring the clinical progression of HIV-1 infection from the asymptomatic stage to the early symptomatic stage and then to AIDS and, eventually, death.

Psychoneuroimmunologic Implications of a Bereavement Support Group in HIV-1 Infection

Given the associations observed between higher levels of social support immediately after a loss and higher levels of NK cell cytotoxicity 6 months later, we developed the bereavement therapy intervention described earlier in this chapter (Goodkin et al. 1996) around the provision of social support (i.e., a supportive group technique). In addition, because life stressor count was shown to be associated with CD4 cell count and proliferative response to phytohemagglutinin, a component of the intervention focused on accurate stressor appraisal and optimal management of bereavement-attendant life stressors. Likewise, because of the association of active coping with NK cytotoxicity in the setting of bereavement, a focus on selection of adaptive coping strategies was incorporated as well.

We designed a study to assess the impact of a bereavement support group intervention on the psychological, immunologic, and health status of HIV-1-seropositive and HIV-1-seronegative men and its mediation by the SSC model described earlier. We hypothesized that the group intervention after bereavement decreases short- and long-term psychological distress. Preliminary data with 83 subjects (50 HIV-1-seropositive, 33 HIV-1-seronegative) indicate that the intervention is beneficial. Multiple measures of emotional adjustment, as well as level of grief, were significantly lower at the

end of the 10-week intervention than they were immediately prior. The mean level of grief, as measured by the Texas Inventory of Grief, decreased from 46 to 38 for HIV-1-seropositive individuals ($P = 0.0001$) and from 44.2 to 37.2 for HIV-1-seronegative individuals ($P = 0.0007$). Total emotional distress, as measured by the POMS, decreased from a mean of 55.7 to 31.3 for HIV-1-seropositive subjects ($P = 0.002$) and from 46.7 to 20.5 for HIV-1-seronegative individuals ($P = 0.006$). Findings for the clinically rated Hamilton Rating Scale for Depression were similar. The mean depression rating decreased from 9.2 to 4.4 for HIV-1-seropositive individuals ($P = 0.002$) and from 10.2 to 6.1 for HIV-1-seronegative individuals ($P = 0.02$). The same pattern emerged when somatic items were deleted from this measure. Clinically rated anxiety, as measured by the Hamilton Anxiety Rating Scale, also decreased from a mean of 8.2 to 4.2 for HIV-1-seropositive individuals ($P = 0.001$) and from a mean of 7.9 to 4.1 for HIV-1-seronegative individuals ($P = 0.01$) (Goodkin et al. 1994a).

Although a final trial evaluation with control groups by serostatus is not possible at this time, the means for control subjects did not show this uniform pattern of decline in emotional distress. In the community comparison standard-of-care control subjects, the only declines observed were in the scores on the Hamilton Rating Scale for Depression (and, then, only when somatic items were included) and the Texas Inventory of Grief. The pattern of data suggested that although some resolution of grief naturally occurs with time, the bereavement support group intervention yields more rapid resolution of the associated emotional distress by facilitating the grieving process and by modifying participants' techniques for managing life stressor burden, improving utilization of social support networks, and increasing use of adaptive (usually active) coping strategies while minimizing use of maladaptive, passive coping strategies.

Despite completion of effective group treatment for a recent, single loss, we also found that somatic anxiety—a measure of life-threat related to health—remained, showing a trend to be positively related to the level of the total number of losses due to AIDS experienced ($P = 0.06$) (i.e., to multiple loss, when there was con-

trol for serostatus). In addition, significant, positive associations were found between multiple loss and hopelessness ($P = 0.01$), loneliness ($P = 0.05$), pessimism about health ($P = 0.01$), and life-threat reactivity ($P = 0.01$) in HIV-1-individuals. When examining the effect of multiple loss in response to our current intervention focused on a single, recent loss, we found that those having multiple losses showed a greater reduction in overall distress but not in grief. The Anger ($P = 0.002$) and Anxiety ($P = 0.04$) subscales of the POMS—which are part of the overall distress measure—were most responsive to the intervention in those with multiple loss. This finding is consistent with the literature describing multiple loss syndrome, and particularly its PTSD-like aspects. One possible explanation for the lack of the expected association with grief (i.e., lack of any effect of the intervention on levels of grief) in those with multiple loss is numbing and denial in the participants with the greatest number of losses, which would mask grief. These data suggest that a therapeutic intervention needs to be directed specifically at multiple loss burden per se, rather than solely at the experience of a recent loss, in order to achieve a maximal effect of a bereavement support group intervention in the HIV-infected population.

We have also completed a pilot study of a bereavement support group for HIV-1-seropositive or at-risk women (Goodkin et al. 1995a). The sample comprised 12 women, all but one of whom were African American. The mean age for the sample was 32.8 years, and the average number of years of education was 12.6. In this sample, the mean number of persons ever known to have died from AIDS was 12.3. Baseline findings revealed that the mean total negative life stressor count for the prior 6 months was 6.6 (impact mean = 14.4), a value well above standardization sample norms. Group attendance was greater than 90%, a rate that was more than the average for our study involving homosexual men (79%). Results from the Group Environment Scale (GES; Moos 1981) for women in this pilot study showed higher cohesion (mean = 9; GES norm = 5.97), higher expressiveness (mean = 7.25; GES norm = 5.6), and lower anger (mean = 0.5; GES norm = 4.9) relative to scale norms for other support groups. Task orientation

(mean = 7.75; GES norm = 5.2) was high, which was an indication of therapist adherence to the semistructured nature of the protocol. After the group intervention, social support availability remained about the same ($mean_{T1}$ = 24.0 [SD = 9.6]; $mean_{T2}$ = 24.8 [SD = 5.5]); however, satisfaction with that support increased ($mean_{T1}$ = 32.0 [SD = 5.6]; $mean_{T2}$ = 33.8 [SD = 2.3]). Bereavement-specific behavioral disengagement (a measure of passive, maladaptive coping) decreased—which was one of the aims of the intervention (M_{T2} = 24.3 [SD = 9.6]; $mean_{T2}$ = 20.0 [SD = 4.6]). Importantly, levels of overall psychological distress (as assessed by the POMS-Total Mood Disturbance score) decreased as well ($mean_{T1}$ = 28.6 [SD = 27.8]; $mean_{T2}$ = 13.2 [SD = 17.1]).

Conclusion

In this chapter, we have shown that the SSC model predictors, particularly life stressors, predicted changes in the CD4 cell count (Goodkin et al. 1992b, 1994b) and, therefore, that immunologic and physical health benefits of the intervention might be expected. Glucocorticoids, which are released in greater amounts in response to psychosocial stressors such as bereavement, down-regulate the production of IL-2 (a Th1 cytokine) and up-regulate the production of IL-4 (a Th2 cytokine) by CD4 cells. Therefore, we predict that the bereavement intervention, by buffering against increments in glucocorticoids, will avert otherwise expected decrements in IL-2 production. The intervention might also protect against decrements in the suppressor-inducer/naive (CD45RA+) subset of CD4+ T lymphocytes, which produce IL-2 and proliferate in response to it in an autocrine manner. Since cortisol has been shown to effect up-regulation of Th2 cytokines (e.g., IL-6, and IL-10 in addition to IL-4)—which is associated with clinical progression of HIV-1 infection—and down-regulation of Th1 cytokines (interferon-γ and IL-12 in addition to IL-2)—which is associated with maintenance of cellular immune function and cytotoxic T lymphocyte activity in HIV-1 infection—these cortisol effects might directly correspond to effects on clinical progression. Moreover,

cortisol has been associated with the induction of apoptosis ("programmed cell death") and, directly, with increased transcription of viral proteins (Clerici et al. 1994). However, an endogenous cortisol antagonist, dehydroepiandrosterone (DHEA), and its sulfated analogue, DHEA-S, should be accounted for in a ratio with cortisol to determine the actual, unopposed in vivo effects of cortisol.

It should be noted that some CD4 cell subsets decrease more rapidly than others throughout the course of HIV-1 infection, perhaps via preferential infection by HIV-1. Although the helper-inducer/primed (CD4+CD45RO+) cell count decreases before any decrements in the suppressor-inducer/naive (CD4+CD45RA+) cell count are seen, later decrements in the latter (and associated decrements in IL-2 production) are likely to lead to decrements in other functional immune measures. These measures include lymphocyte proliferation in response to phytohemagglutinin and pokeweed mitogen (a T cell–dependent B cell mitogen), NK cell cytotoxicity, and killing of HIV-1-infected cells by activated (HLA-DR+) cytotoxic (CD11a+^{bright}) CD8+ T cells. The last-mentioned measure has been shown to be associated with long-term nonprogression (Cao et al. 1995). Decrements in such cellular immunologic measures would be expected to be associated with increased viral load, which promotes disease progression.

We also predict that the support group intervention for bereaved HIV-1-seropositive and HIV-1-seronegative homosexual men is effective, in part, because it serves as a buffer against predicted decrements in the production of IL-2 and IL-2 receptor mRNA in response to anti-CD3 monoclonal antibody stimulation of T lymphocytes. Of note, Glaser and colleagues (1990) studied examination stress, which, like bereavement, would be expected to be associated with increased glucocorticoid secretion and decreased IL-2 production. However, the authors unexpectedly demonstrated increased IL-2 with decreased IL-2 receptor mRNA and IL-2 receptor expression. These data suggest that the modulation of IL-2 receptor expression might not be explained solely by changes in IL-2 and cortisol levels, but might, in fact, be mediated by an alternative neuroendocrine mechanistic pathway (e.g., the sympathetic adrenomedullary system).

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Chapter 11

Psychoneuroimmunology: Perspectives of an Immunologist

Cobi J. Heijnen, Ph.D.

Whether one is for or against research on stress and the immune system: deep inside everybody knows that life stressors, either acute or chronic, influence the functioning of the body. In recent years, many scientists have demonstrated experimentally that environmental factors influence the immune system (Ader et al. 1991). The communication between the two systems is effected, on the one hand, by neuroendocrine signaling molecules that transfer information from the neuroendocrine system to the immune system (Blalock 1985) and, on the other hand, by various products of the immune system, especially cytokines, signaling the brain and thereby influencing behavior (Dinarello 1988).

The hierarchy of the mediators that represent the pathways by which the target organs can receive the stressor signals from the environment is not yet known. We do know, however, that short-lasting emotional or physical stimuli can immediately influence the immune system (Brosschot et al. 1992; Croiset et al. 1987). When an individual is exposed to bicycling for 5 minutes, we can immediately observe an enhancement of the immune response at the levels of specific cytokine production and natural killer (NK) cell activity. At the same time, the proliferative response of T cells decreases as a result of this type of physical stressor. A short-lasting psychological stressor—for example, solving a puzzle—causes the same effect, although less pronounced, on the immune system within 5 minutes. The number of NK cells in the peripheral circulation, as well as the activity of NK

cells, increases (Brosschot et al. 1992).

The mechanism by which the immune response is acutely modulated is still a matter of debate. Catecholamines and cortisol have both been proposed as the important mediators of such immunomodulation. Indeed, exposure of rats to experimental stressors has shown that both of these neuroendocrine mediators are operative in the modulation of the immune response. However, in humans, the effects on the immune system of an acute stressor are not mediated by cortisol, but rather, for the greater part, by catecholamines. Our group investigated the effects of β-adrenergic blockade on immunologic and cardiovascular changes induced by mental stressors in humans. We clearly showed that mental stressors induce activation of the sympathetic nervous system, with concomitant increases in both the number of NK cells in the circulation and NK cell activity. All of these changes have been inhibited by the β-blocker propranolol (Ader et al. 1991). This study underscores that in humans catecholamines are responsible for the cell trafficking that occurs after an emotional stressor as well as for changes in cell function.

To investigate an immunomodulatory effect of cortisol, we administered a bolus (1 μg/kg) of corticotropin-releasing hormone (CRH) to healthy volunteers. Healthy human subjects were injected intravenously with CRH. Before and after CRH administration, blood was drawn via an intravenous catheter. T cell proliferation after activation with the T cell mitogen phytohemagglutinin, along with plasma cortisol levels, was determined. The cortisol response and the immune response were monitored over several hours. As the results in Figure 11–1 clearly show, there was a pronounced increase in cortisol levels. However, there was no apparent influence on the immune system. Thus, acute and transient changes in cortisol do not alter the activity of the immune system. These results demonstrate that one has to be careful when comparing animal studies and human studies with regard to the role of corticosteroids. Humans may be less sensitive to modulation of peripheral blood immune responses by cortisol than rats.

The possibility remains that stressor-induced cortisol increases can enhance the sensitivity of the immune system to catecholamines, since it has been shown that cortisol can mediate an up-

regulation of β_2 receptors in vitro. Stressors of a more chronic nature are often associated with chronic increases in cortisol, which do affect immune responsiveness. We have preliminary evidence that the basal level of cortisol correlates with the basal level of NK cell activity. Moreover, administration of prednisolone for a week changes the sensitivity of the immune system to cortisol considerably. This implies that cortisol is important for maintaining the basal metabolic status of the immune system.

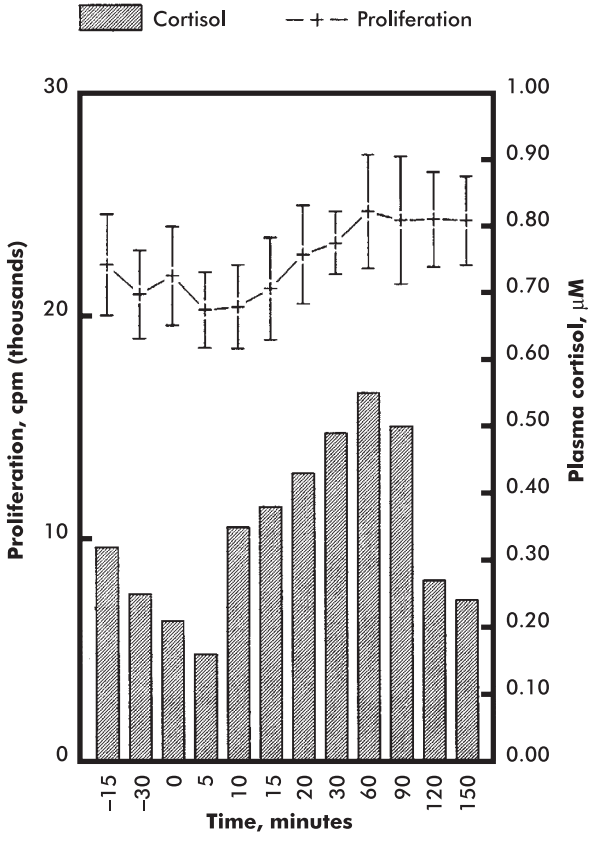

Figure 11–1. The effect of corticotropin-releasing hormone (CRH)–induced increases in cortisol on immune reactivity in healthy human volunteers ($N = 6$). T cell proliferation after activation with the T cell mitogen phytohemagglutinin, as well as plasma cortisol levels, was determined.

Is a Stressor Salutary or Deleterious?

The simplistic question of whether a stressor is salutary or deleterious is often asked and can be approached from the psychoneuroimmune perspective on three levels.

Basal Level

To maintain a homeostasis, one's body needs to be "tuned" to various mediators of the neuroendocrine system. Therefore, it is salutary that the neuroendocrine system is sensitive and reactive. It is also salutary that the immune system is sensitive and reactive to neuroendocrine stimuli. When a person is no longer reactive to, for example, catecholamines, the capacity to down-regulate response to a bacterial infection is diminished. This situation is often encountered in patients with active inflammatory autoimmune diseases like rheumatoid arthritis. In view of these data, it is tempting to hypothesize that a decreased reactivity of the immune system to catecholamines may negatively influence the course of the disease.

Acute Stressors

Acute stressors cause only minor disturbances in the homeostasis of the body. The immune system possesses nonsaturated receptors for catecholamines and reacts mildly and transiently. Acute stressor stimuli may nevertheless affect health when a person is already "at risk" because of high chronic exposure to severe stressors, such as occurs with chronic pain or during shifts in group dominance hierarchies (e.g., job stressor). It is feasible that in these situations a moderate acute stressor changes the balance even further—a shift that may have deleterious effects for the organism.

Chronic Stressors

Chronic stressors can be deleterious for maintaining the integrity of the body and may affect health. In an earlier study, we showed that the effects of major life events are less pronounced than the effects of daily repeating stressors. One of the important results of

the study is that it was the perceived controllability of the stressors, and not the number of these daily repeating stressors, that determined the effect on the immune response (Brosschot et al. 1992, 1994). One of the earliest studies on the effects of a chronic stressor on the immune system was that of Glaser and colleagues (1987). These authors showed that examination stress can affect health. They measured the immune response to Epstein-Barr virus (EBV) on the level of specific antibodies, as well as the cytotoxic T cell response to EBV in combination with subjective health parameters. They found that examination stress causes an increase in the serum titer of EBV antibodies and a diminished capacity of the individual to generate EBV-specific cytotoxic T cells that can kill virus-infected cells in the body (Glaser et al. 1987).

Perinatal Stressors

As mentioned earlier, acute stressors represent only minor disturbances for the immune system. However, there is an exception to this situation. During ontogeny, the neuroendocrine system and the immune system develop in mutual dependence. Consequently, dysregulation in one of these systems induces changes in the other. In rats or monkeys, exposure to an acute stressor just before or after being born can cause static and long-lasting changes in the neuroendocrine system, the behavior, and the immune system of the animal (Coe et al. 1989; De Kloet et al. 1988). When the animal is, for example, separated from the mother for a short period of time during a few consecutive days, the consequences of this stressor are still present during the adult life of the animal. On the level of the immune system, the animal's capacity to mount a specific antibody response, as well as NK cell activity, is decreased in comparison with the immune response of animals that have not been separated from the mother.

Our own preliminary experiments also indicate that neonatal stress can influence the sensitivity of the animal for induction of autoimmune diseases like rheumatoid arthritis. The mechanisms by which these disturbances are induced apparently derive from a disturbance of neural homeostatus set-points in the brain. One of the conse-

quences of this change in neural homeostatic set-point is a decreased secretion of corticosterone after exposure to a stressor in adult life (Coe et al. 1989; De Kloet et al. 1988). It is remarkable that the effects of the perinatal stressor can be mimicked by the administration of glucocorticoids just before birth. These data raise the question of what consequences prenatal glucocorticoid administration to human fetuses have on the neuroendocrine and immune system of the developing child. The administration of glucocorticoids is often necessary to support maturation of the lung in a premature birth. Children in this situation often express behavioral disturbances when they grow up and have an increased risk of infection. It is an intriguing question whether the mechanisms responsible for these symptoms are the same as those described earlier for the rat and monkey. In view of the above-mentioned data, it is also important to investigate the consequences that exposure to stressors immediately after birth (e.g., being in an intensive care unit) have for the development of the child. If the symptoms observed in the rat and monkey are applicable to the human situation, one is obliged to concentrate research on the effects of stressor prevention in this precarious neonatal period.

In summary, perinatal experiences may influence the development of the immune system and may have far-reaching and long-lasting consequences for immune reactivity at a later age. Conversely, early dysregulation during the development of the immune system—for example, a failure of tolerance induction to a specific autoantigen—may have implications for the development of the nervous and endocrine systems, thereby influencing the expression of emotions, behavior, and disease in later life.

Relation Between the Sympathetic Nervous System and Disease

The sympathetic nervous system interacts with the immune system through the local release of norepinephrine by sympathetic postganglionic efferent neurons and through the secretion of epinephrine by the adrenal gland. Lymphocytes and macrophages have β_2-adrenergic receptors, and both epinephrine and norepinephrine exert their regulatory influence on immune cells via these

receptors (Bisphoric et al. 1980). Under normal physiological conditions, β_2-adrenergic agonists, like catecholamines, inhibit many functional immune responses (Arnason 1992). They inhibit T cell proliferative responses and down-regulate IL-2 receptors on activated T cells (Feldman et al. 1987) as well as IL-2 production (Crary et al. 1983). Moreover, catecholamines inhibit B cell proliferation and antibody secretion, as well as, under certain circumstances (e.g., when cell count is controlled or in the setting of chronic stressor exposure), cytotoxic T cell and NK cell functional responses (Burchiel and Melmon 1979; Hatfield et al. 1986; Kouassi et al. 1990). Besides having a direct effect on functional immune responses, catecholamines influence the sensitivity of leukocytes to neuropeptides and other neurohormones (Kavelaars et al. 1990). Through these mechanisms the autonomic nervous system exerts a regulatory influence on the immune system. An unresponsiveness of leukocytes to catecholamines should theoretically lead to uncontrolled, flamboyant immune responses, as is the case in chronic inflammatory conditions such as rheumatoid arthritis.

Juvenile Rheumatoid Arthritis

Autonomic dysfunction has been extensively described in rheumatoid arthritis. The methods used in these investigations were dynamic autonomic function tests such as cardiovascular tests during orthostatic stress (Leden et al. 1983), the Valsalva maneuver (Leden et al. 1983), deep breathing (Perry et al. 1989), measurement of pupil size (Perry et al. 1989), and perspiration (Han et al. 1988; Nakayama 1988).

We performed a study of autonomic dysfunction in children with juvenile rheumatoid arthritis (JRA). JRA is characterized by a chronic inflammation of one or more joints. Three subtypes have been described: monoarticular arthritis, polyarticular arthritis, and a systemic form of the disease. In addition to the inflammation of the joints, systemic JRA is accompanied by an intermittent fever lasting at least 14 days and can involve hepatosplenomegaly, pericarditis, pleuritis, and lymph node enlargement. JRA is also

characterized by symptoms such as general malaise, decreased appetite, increased perspiration, increased pain sensitivity, changes in blood pressure and heart rate, and sleep disturbances. Apart from these somatic symptoms, the disease is accompanied by behavioral disturbances such as increased attention focused on surroundings, increments in nonspecific arousal, attention disorders, inhibition of ongoing behavior, and depressive moods.

To establish the role of the autonomic nervous system in JRA, cardiovascular autonomic tests during orthostatic stress were performed in 31 children with JRA and 68 healthy children (Bennhagen et al. 1987; De Jong–de Vos van Steenwijk et al. 1995; Nakayama 1988). Altered autonomic function was shown in all onset-types of JRA. The autonomic changes were increased systolic and diastolic blood pressure before and after the orthostatic stress and an increase in peripheral vascular resistance. The dysregulation of the autonomic nervous system was most pronounced in children in the subgroup with active systemic arthritis.

We investigated the consequences of dysregulation of altered autonomic function for the immune system. When peripheral blood cells of healthy children are incubated with epinephrine, one can observe an increase in the second messenger, intracellular cAMP. In general, increases in cAMP lead to a down-regulation of the immune response. However, in our study, after incubation of peripheral blood mononuclear cells with epinephrine, no increase in intracellular cAMP was observed in peripheral blood cells of children with active systemic and polyarticular JRA, whereas there was an increase in intracellular cAMP in the peripheral blood cells of age-matched control subjects under these conditions. Thus, in children with active systemic and polyarticular JRA, catecholamines cannot display their normal regulatory activities. Under these circumstances, the changed sensitivity of the immune system to catecholamines may lead to unregulated immune responses, which can have negative consequences for the chronic expression of arthritis. It is unknown by which factors the autonomic nervous system is dysregulated under chronic inflammatory conditions. Pain (Koltzenburg and McMahon 1991) and psychosocial factors (Weiner 1991), as well as the inflammatory process itself (Bese-

dovsky and Sorkin 1977), are known to be capable of dysregulating autonomic function. It is hoped that future research will give more insight into this phenomenon.

Future Perspectives

In view of the results described in the previous section, the question arises, Is it possible to treat inflammatory autoimmune diseases by trying to normalize autonomic dysregulation? Most of the time, patients with systemic and severe polyarticular JRA no longer respond to conventional therapy with corticosteroids. Therefore, it is of utmost importance to find a new strategy for therapy: tuning of the autonomic nervous system through behavioral and drug therapy.

One obvious approach in such cases is relaxation training. It has been shown that progressive muscle relaxation and autogenic training have normalizing effects on the autonomic nervous system. After relaxation therapy, the muscle tone decreases, as does the basal blood pressure. Children with JRA report a reduction in pain after relaxation therapy. Also, in other inflammatory diseases, relaxation training leads to a reduction of catecholamine secretion and an improvement in clinical status. Although relaxation training and other behavioral interventions have been proven to be useful, they do not completely cure the disease. In children with JRA, the immune system no longer reacts to catecholamines with a sustained increase in cAMP. To treat patients with inflammatory autoimmune diseases effectively, it is necessary for immunologists and mental health specialists to work in a truly interdisciplinary way by supporting use of relaxation training with pharmacologic treatment regimes—for example, cAMP-enhancing drugs like phosphodiesterase inhibitors (e.g., theophylline). In this way, psychoneuroimmunology may be capable of contributing to the therapy for many chronic diseases.

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This book was originally conceived as an extension of a symposium on psychoneuroimmunology presented at the annual meeting of the American Psychiatric Association. The symposium consisted of presentations in the areas of behavioral genetics, the relationship between stressors and immunity in a medically healthy population, and the effects of stressors on immune function in specific populations of patients—those with major depressive disorder, cancer, and HIV/AIDS. . . .

When the work presented at this symposium was first offered for consideration for publication in the *Progress in Psychiatry* series, we decided that a considerable extension of the scope of the symposium was warranted. One of the aspects chosen for inclusion was the role of psychoneuroimmunology in carcinogenesis and established tumor progression. . . . A second area in which the focus of the book was expanded is that of the role of psychoneuroimmunology in HIV infection and AIDS.

Psychoneuroimmunology: Stress, Mental Disorders, and Health exemplifies an intensive focus on the psychoneuroimmunology research questions applied to the example of one specific disease process. This level of detail is required for the satisfactory application of this area of research to immunologic changes in patients with other diseases and for determination of the clinical relevance of any such immunologic changes that might be related to psychosocial factors.

Karl Goodkin, M.D., Ph.D., from the Introduction

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