Psychoneuroimmunology: A Basis for HIV Treatment
Jeffrey M. Leiphart, PhD

What is psychoneuroimmunology? What research exists supporting psychoneuroimmunology (PNI) as an approach to treating people with HIV disease? Is the scientific community ready and able to develop and implement PNI-based clinical protocols as immune-boosting treatment for people with HIV disease? This article looks at these questions and concludes that, after years of research, psychoneuroimmunology not only stands ready to produce effective clinical treatments as appropriate adjuncts to primary medical care, but has already begun to do so.

What is psychoneuroimmunology? The word psychoneuroimmunology can be taken literally, meaning that the psychological self interacts with the nervous system which, in turn, interacts with the immune system. In popular culture, this connection between our psychological lives and our physical health is expressed as the “mind-body connection,” and is reflected in everyday speech: “Don't stress out, or you'll get sick,” or “You'd better slow down, or you'll burn out and get sick.”

The language of medical science is more complex. For example, according to PNI researchers George F. Solomon, Margaret Kemeny, and Peter Anton, psychoneuroimmunology is a "transdisciplinary" field:

Its clinical aspects range from an understanding of the biological mechanisms [that underly] the influence of psychosocial factors on the onset and course of immunologically-resisted and mediated diseases, to an understanding of immunologically-induced psychiatric symptoms... Psychoneuroimmunology aims at clarifying the scientific basis for humanistic medicine and at developing new models of health and illness.1

Psychoneuroimmunology, a 30-year old medical research specialty, started in the mid-1960s, when Solomon studied chronic rheumatoid arthritis and found that certain personality characteristics were associated with disease severity and progression. These early findings have been replicated by various researchers. The field gained widespread acceptance in 1975 following Robert Ader and Nicholas Cohen’s classic study showing that immunosuppression could be behaviorally conditioned.2 Since then, PNI research has led to both theoretical models and hundreds of published experimental studies demonstrating a connection among psychological factors, immunity, and health status.3

Psychoneuroimmunology and HIV Disease

Given that AIDS, by definition, is an immune deficiency, it was only natural that PNI researchers began to study it in the mid-1980s. Over the past 10 years, there has been an explosion of HIV-related PNI research at major universities around the world.

PNI research shows that certain psychological states lead to HIV disease progression and diminish longevity, while others enhance immunity and long-term survival. Among the factors determining these states are: degree of fatalism regarding HIV status; intensity and longevity of stress, grief, or depression; awareness of life purpose and goals; self-assertive ability; availability of trusted social support; degree of "outness" regarding gay identity; crisis coping capacity; and behavioral body-care patterns such as appetite and nutrition, sleep, toxin intake, and physical exercise. Some of these immune-suppressing cofactors can be induced by the realities of living in an unrelenting public health crisis: fear and panic.
Cofactors were a big deal 10 years ago, when so little could explain why some people with AIDS got sick and others didn’t. (Of course, eventually most others did get sick; it just took longer). We hypothesized co-factors everywhere—poor nutrition, poor sleep, lack of exercise, cigarette smoking, drug use, stress, depression, ability to cope—the list of contenders went on and on as people desperately searched for explanations.

Today, especially over the last two years, when studies have found huge reservoirs of HIV in the lymph nodes and other parts of the body, when antiviral treatment is remarkably effective in stopping progression, and when there is evidence that non-progressors may actually be infected with ineffectual virus, the apparent role of cofactors as central agents in HIV progression has diminished.

**Significant Effects?**

But if cofactors are no longer necessary for HIV progression—they are not even called co-factors anymore—they may still play a role in health and the HIV-related deterioration of the immune system.

That’s what Jeffrey Leiphart and Steve Cole suggest. Together they provide data demonstrating that there is a relationship among mental health, neural functioning, and immunity, from which arises the field of psychoneuroimmunology. The biological connections among these systems is fairly well-established. What is not as clear is whether the effects of these connections are strong enough to suggest clinical applications. For example, if therapists help clients reduce stress, will this have a significant effect on physical health, particularly among people with HIV disease? In addition, in the brave new world of protease inhibitors and combination therapy, has psychoneuroimmunology diminished in importance, and is it possible to measure the effects of psychoneuroimmunology in people who are on antiviral drugs?

**Beyond Mental Health?**

While there are no clear answers to these questions, several sites around the country are using the accumulated data to formulate programs to help people with HIV maintain psychological equilibrium based on the hypothesis that this will slow disease progression. And because of the obvious relationships between psychotherapy and factors like stress, depression, and coping mechanism, it may be that counseling will have effects far beyond improving mental health.
disease suggests practical approaches to improve both immune functioning and health of HIV-infected individuals. But the question of whether the medical and psychological communities are ready to apply this research to practical interventions is at the core of a debate among PNI researchers. On one hand, some researchers believe that we do not yet know enough about the mechanisms of psychological influence on immunity and disease progression to develop safe and effective interventions. This position was clearly articulated recently by Robert Ader. He argued that although PNI research has accumulated important information, the results of this research are not yet sufficient to develop clinical treatments.

On the other hand, researchers like George Solomon believe it is time to move PNI "out of the research lab and into the clinics." He highlights evidence that psychological states can impact immunity, that long-term survivors of HIV disease have certain psychological characteristics in common, and that those very characteristics are known independent of HIV-related research to affect the immune system in a beneficial way. Solomon argues that the convergence of data from these three lines of research inquiry provides a sufficient basis for developing treatment protocols, as long as treatment is rigorously evaluated. He adds that psychological factors can be endorsed as shaping treatment only after research demonstrates their significant impact on both immunity and health outcome.

**Clinical Programs**

In the past few years, clinicians have begun to create HIV-related PNI programs, and implemented these clinical programs at the University of Miami, the San Diego Lesbian and Gay Men’s Community Center, and Harvard University. While each of these “start-up” programs emphasizes different PNI-related issues and program structures, it is noteworthy that they represent a broad consensus about program content and structure.

The University of Miami Center for Biopsychosocial Studies of AIDS provides three types of PNI-based clinical interventions for seropositive individuals. First, Cognitive Behavioral Stress Management employs a 10-week group intervention to teach participants effective stress reduction skills through adaptive coping strategies, anger management and assertion skills, increased social ties, and relaxation training. Results of the program show that participants significantly decreased levels of depression and anxiety, increased social support and use of effective coping strategies, and showed improvements in immune functioning. Second, an Aerobic Exercise Training Intervention emphasizes aerobic fitness using moderate bicycle exercise (three 45-minute workouts per week). Results show that this routine provides seropositive participants with a buffer against immune decrements (decreased natural killer cell levels) that typically follow an acute emotional stressor.

Third, a Bereavement Support Group Intervention consists of 10 weekly group sessions, and incorporates both open discussion and structured topics to help clients express grief and re-engage with life. Longitudinal evaluation has shown that participants achieved decreased levels of psychological distress and grief, increased levels of CD4 cells and mitogen response to PHA, and positive health outcomes as measured by decreased health-care use.

The San Diego Lesbian and Gay Men’s Community Center runs a mental health program designed specifically to boost immunity, with much of the program content based on PNI research results. The L.I.F.E. Program (an acronym for Learning Immune Function Enhancement) teaches seropositive participants to self-manage 19 cofactors that are known to affect health, immunity, or HIV disease progression. The cofactors are: fatalism, internal speediness (chronic impatience), survival-related stress, grief and loss, depression, life purpose and goals, self-assertive ability, trusted support, crisis coping capacity, breathing patterns, water intake, appetite and nutrition, sleep, toxin intake, physical exercise, exposure to infections and re-exposure to HIV, body care routines when sick, knowledge about HIV-related health issues, and medical care relationships.

Clients undergo three phases of treatment spanning a full year: a three-month psychoeducational group process, followed by three months of individual “cofactor counseling,” followed by a six month L.I.F.E. Support Group. Clinicians assess clients in terms of performance for each cofactor, develop a profile indicating strong and

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**References**


weak cofactor performance areas, and help clients to formulate maintenance strategies for strong cofactors and remedial plans for weak ones. Initial outcome research demonstrates that clients who complete the program improve their psychological quality of life and reduce the number of HIV-related symptoms. The combination of peer support and the individualized planning of cofactor counseling seems to be the critical aspect of this program.

The Harvard Medical School operates a behavioral medicine clinical program called the Mind/Body/Spirit Program for HIV/AIDS. This treatment intervention provides seropositive individuals with 10 weekly, two-hour group sessions that focus on a range of psychological issues, each selected because of its robust presence in behavioral medicine research. Topics include: stress (covering anxiety, depression, loneliness, anger, grief) and its impact on immunity; hardiness and resilience and their relationship to commitment, control, life goals, and volunteerism; cognitive restructuring achieved by challenging negative thoughts; physical exercise focusing on yoga; nutrition, including general education with referral to individual nutritional counseling when indicated; journal writing, focused on the immune-boosting effects of emotional expression via writing; spirituality, exploring the nature of hope; and humor, emphasizing the immunological and health benefits of laughter. Ongoing evaluation shows that clients completing the program experience significant reductions in the number of both psychological and physical symptoms.

Conclusions

The medical science of psychoneuroimmunology has generated a significant body of research showing relationships among psychological functioning, immunity, HIV disease progression, and longevity. Based on this research, clinicians have crafted psychological treatments designed to change behavior, enhance immunity, moderate symptoms, and increase longevity. These interventions have various benefits when compared to standard medical treatments: they are non-toxic, have no negative side-effects, are relatively inexpensive to deliver, and empower seropositive individuals to participate in their own treatment.

PNI-based immune-boosting treatments are natural partners with primary medical care. The promising results of the new antiviral combinations do not eliminate the need for simultaneous treatment aimed at boosting immune system efficacy. In a recent article, Anthony Fauci notes that the “host factor” of immune competence predicts disease progression, and argues that optimal treatment includes both antiviral and immune-boosting therapies. The research results, plus the emergence of psychological treatment programs throughout the world, suggest that comprehensive clinical trials of PNI-based approaches might lead to improved longevity and quality of life for people with HIV disease.

Clearinghouse: PNI and AIDS

References


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The Biological Basis for Psychoneuroimmunology
Steve W. Cole, PhD

How do psychological states influence the biological processes involved in physical health and disease? The brain and the immune system are linked by two major physiologic systems: the sympathetic nervous system and the hypothalamic-pituitary-adrenal system. These two systems influence a wide variety of physiologic processes, including cardiovascular function, brain function, muscle function, digestion, respiration, metabolism, reproduction, and growth. But it is their effect on the immune system that is most relevant to HIV disease and HIV-related care.

The sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal system (HPA) both play roles in the normal function of the body, but become particularly active during stressful or emotional circumstances. These experiences are associated with increased activity in the brain's limbic system, whose nerve cells then activate the SNS and the HPA. The SNS and HPA probably evolved to “retune” the body's functioning during natural emergencies such as attacks by predators, famine, injury, and extreme weather conditions. However, when these systems activate in the absence of any need for physiologic retuning—when someone is hassled at work, worried, or grieving—they may needlessly hamper the body's ability to defend itself.

The Sympathetic Nervous System

The SNS is a network of nerve cells running from the brain stem—the evolutionarily “older” part of the brain that controls the body’s physiologic systems—down the spinal cord and spreading out into the body to contact a wide variety of organs. These nerves also penetrate into the sites where immune system cells develop and respond to pathogens, including the bone marrow, thymus, spleen, and lymph nodes. SNS nerves become particularly active in “fight or flight” situations and other circumstances in which a person strives to respond to a challenge.

Activated SNS nerves release a chemical neurotransmitter called norepinephrine and SNS nerves penetrating into the adrenal gland can also cause the release of epinephrine (adrenaline). Norepinephrine and epinephrine bind to beta2 adrenoreceptors present on the surface of many immune system cells. Among these cells are: monocytes and macrophages, which engulf pathogens and signal their presence to the rest of the immune system; NK (“natural killer”) cells and CD8 (“cytotoxic”) cells, both of which detect and destroy virally infected and some cancer cells; B cells, which produce the antibodies critical to destroying bacteria and other pathogens that live outside cells; and CD4 cells, which coordinate the response of the rest of the immune system.

Many immune system cells change their behavior in the presence of epinephrine or norepinephrine. For example, under laboratory conditions, NK cells and CD8 cells become less effective at killing target cells. Norepinephrine can retard the ability of NK, T, and B cells to multiply in response to a pathogen. It can also reduce the mobility of macrophages and shunt some types of immune cells into circulation and other types out of circulation and into the spleen, lymph nodes, thymus, and bone marrow. Epinephrine is so effective at suppressing

The body clearly contains the physical hardware to permit the brain to influence immune function.

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See also references cited in articles in this issue.
some types of immune responses that physicians use it to treat patients suffering from excessive immunologic activation such as bee-sting allergies. However, SNS activation does not suppress all immunologic responses. Under laboratory conditions, norepinephrine or epinephrine can increase the production of antibodies and increase ability of macrophages to signal the presence of a pathogen.

In general, research suggests that SNS activation can reduce the “cellular immune response,” by which the immune system destroys pathogens living inside cells (for example, viruses like HIV), while sparing or enhancing the “humoral immune response,” by which it destroys pathogens living outside cells (for example, bacteria).

Hormonal Systems

The HPA system links the brain and body via a network of circulating hormones. HPA activation begins in the hypothalamus, an area of the brain that governs many “housekeeping” processes, including temperature regulation, thirst, and hunger. Under conditions of overwhelming stress—“giving up” or “defeat,” as opposed to the “active coping” that activates the SNS—the hypothalamus increases its release of corticotrophin releasing factor (CRF) into a small network of blood vessels that descend into the pituitary gland. In response to CRF, the pituitary gland synthesizes adrenocorticotropic hormone (ACTH), which travels through the bloodstream down to the adrenal glands and triggers the release of cortisol into circulation.

Cortisol is a steroid hormone that has numerous effects on a wide variety of physiologic systems. Much of cortisol's effect on the immune system stems from its ability to alter the production of chemical messengers called cytokines, which coordinate the actions of the various cells involved in an immune response. Like norepinephrine and epinephrine, high levels of cortisol can suppress the cellular immune responses critical to defending against viral infections. In fact, physicians often administer a synthetic analog of cortisol to suppress the excessive immune system responses involved in autoimmune diseases such as rheumatoid arthritis and allergic reactions. Cortisol can also prompt some immune system cells to move out of circulating blood and into lymphoid organs.

Some aspects of immune function can also be altered by other hormonal systems, including those involved in growth and regeneration of the body's cells (growth hormone), reproduction (for example, estrogen and prolactin), and pain (for example, beta-endorphin). The brain influences the activity of these hormonal systems, and psychological states can alter their function.

Conclusion

The body clearly contains the necessary physical hardware to permit the brain to influence immune function. What is less clear is how large such influences are and how significant they might be for the physical health of seropositive individuals. Animal studies indicate that extreme psychological stress can exacerbate viral infections by suppressing cellular immune responses. Ethical concerns rule out such studies in humans, and the absence of good animal models of HIV infection make it difficult to determine what role psychoneuroimmunologic interactions might play in this context.

Much remains to be learned about psychoneuroimmunology. Several controlled studies have shown that certain psychological characteristics are associated with differences in the rate of HIV progression. But determining whether these effects might be mediated in part by the activity of the SNS and HPA is complicated by the fact that many critical processes take place in the lymph nodes, spleen, and bone marrow—tissues that are difficult to access. It is also complicated by the fact that we do not know exactly which biological factors determine how quickly HIV disease progresses and thus which to study. In addition, because the intensity of HPA and SNS activity differs across individuals as a function of temperament and stress, it is likely that the magnitude of PNI effects and the effect of PNI interventions will vary. Finally, HIV infection progresses over a relatively long period of time, requiring long (and expensive) studies to identify factors influencing disease.

References


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Recent Reports

Depressive Symptoms and HIV Progression

Depressive symptoms seem to be associated with a slightly increased risk of herpes simplex virus (HSV) recurrence and increased self-reports of HIV-related symptoms, according to a statistical review of the literature on these diseases. Depressive symptoms, however, are not associated with accelerated HIV progression. In addition, psychological stressors seem not to be associated with recurrence of HSV or with HIV symptoms or progression.

The authors reviewed 16 studies on HSV and 19 studies on HIV. Although they did not clearly define "depressive symptoms" or "stressors," they noted that data from the 35 studies was based on self-report questionnaires. For HSV studies, the mean age of participants was 27.9 years, 87 percent were White, and 80.2 percent were female. For the HIV studies, the mean age of participants was 35.5 years, 83 percent of participants were White, 0.9 percent were female, and 95.8 percent were gay or bisexual.

Although statistical analyses across all studies appeared to indicate a relationship between stressors and HSV viral recurrence, those studies with better designs did not in fact observe greater HSV recurrence in the wake of stressors. Depressive symptoms, on the other hand, did predict episodes of HSV. Characteristics of study participants seemed to affect the relationship between psychological factors and HSV recurrence: studies that excluded medicated patients and that focused on a predominantly female population observed a weaker relationship between psychosocial factors and HSV recurrence. Studies that focused on older subjects found a weaker connection between stressors and HSV recurrence than studies that included younger subjects.

With respect to HIV studies, depressive symptoms, but not stressors, were associated with increased reporting of HIV-related symptoms. Again, participant characteristics seemed to moderate this result. Studies of younger and more racially diverse groups tended to observe a stronger relationship between depressive symptoms and self-reported HIV symptoms. In general, depressive symptoms were not associated with clinically defined HIV progression or increased morbidity measured by CD4 cell changes or other immunological markers. However, disease stage may influence the relation between depressive symptoms and HIV-related symptoms; studies that included people with AIDS tended to observe correlations between depressive symptoms and reduced CD4 cell counts. The authors suggest that this relationship might more accurately reflect distress over deteriorating health than a causal connection. Finally, while the correlations cited are small, the authors speculate that reactivation of the herpes virus concurrent with depression may accelerate HIV progression for people infected with both viruses.

Psychoneuroimmunological Study Limitations
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According to a review of the literature, the relationship between HIV disease and psychoneuroimmunology (PNI) remains unclear because of the limitations of study methodologies and an inadequate understanding of immunology and HIV disease. By examining the four types of studies used in PNI research—cross-sectional studies, longitudinal investigations, intervention studies, and studies of long-term survivors—these limitations become most apparent.

Most cross-sectional investigations examine, at a single point in time, the relationship between measures of immune system efficacy and specific psychosocial variables such as depression or social support. Such research, by its nature, however, contributes little to an understanding of causal relationships. Cross-sectional studies are particularly vulnerable to confounding factors such as nutritional status, sleep patterns, exercise, and recreational drug use, which may distort immune function. In addition, a measure such as a CD4 count has little meaning unless researchers establish time of infection and different rates of progression. Finally, many cross-sectional studies erroneously assume that seropositive subjects are under emotional distress.

Longitudinal studies typically examine the relationship between psychological measures and immune function, permitting, because they occur over time, some investigation of cause and effect. The best studies occur over long observation periods and calculate rate of immune decline in relationship to baseline measures of
immune function and emotional distress. Even these studies can be flawed: three well-designed studies that met these guidelines had contradictory results regarding depression and CD4 cell levels. Furthermore, since mood fluctuates over time, comparing measures of emotional distress with immune function can be problematic.

Intervention studies are used primarily to demonstrate whether stress affects the immune systems of people with HIV. Researchers monitor emotional distress and immune function in conjunction with a naturally occurring or experimentally manipulated event—the intervention—and compare their results with a matched control group that has not undergone this intervention. The most common stressor investigated is HIV antibody testing and serostatus notification. For example, a researcher might study the effect of serostatus notification on immune function by measuring CD4 cell counts in two groups: a control group and subjects undergoing exercise or cognitive behavioral stress management interventions.

Cross-sectional studies of long-term survivors enable researchers to identify the psychological characteristics—for example, problem-solving skills, social support, and active coping—associated with enhanced survival. But these studies have been limited by their failure to use a common definition of long-term survival and because none has taken into account the immunological, virological, and genetic factors that affect survival. Further, these studies have not adequately addressed the confounding effects of antiviral medications.

**Death of a Partner**


In a small study of gay men in Los Angeles, the death of an intimate partner led to immune changes in seropositive men. In addition, while levels of depression among bereaved men did not correlate with these immune changes, depressed mood in a sample of non-bereaved seropositive men was significantly associated with diminished CD4 cell counts and higher percentages of activated lymphocytes.

Researchers recruited 39 men who reported the death of an intimate partner in the previous 13 months and a matched control group of 39 men who had not experienced such a loss. In each sample, 21 men were seropositive and 18 men were seronegative. None of the participants in the study had AIDS and none was taking zidovudine (ZDV; AZT). The mean age of the 78 men was 38 years, and most were White. Researchers recruited participants from the Natural History of AIDS Psychosocial Study, a subsample of the Multi-Center AIDS Cohort Study's Los Angeles site.

Researchers analyzed two blood samples for each participant: one drawn before the partner's death and another drawn within 13 months after the death. They analyzed samples taken over a similar time period for control subjects. The study also assessed and controlled for behavioral factors such as recreational drug use, alcohol consumption, cigarette smoking, exercise, sleep loss, and sexual behavior.

Sero-positive bereaved men exhibited a significant increase in levels of neopterin—which has been shown to be a strong predictor of development of AIDS—and a significant decrease in the proliferative response to PHA, a similar predictor. There were no significant differences over time in CD4 cell counts, the expression of activation markers on lymphocytes, or serum levels of beta2 microglobulin. Seronegative bereaved men exhibited no immune changes. Finally, researchers caution that the failure to correlate HIV progression and depression in bereaved men may have resulted from a failure to differentiate appropriately between grief and depression.

**Next Month**

The range of psychotherapeutic approaches continues to expand, and many therapists are more eclectic in their approaches than they are committed to a single conception. In the March issue of *FOCUS,* **Stephanie Sabar, LCSW,** a social worker with Los Angeles Jewish AIDS Services, discusses the ways in which Gestalt therapy is most fruitfully applied to treating clients with HIV disease. Gestalt therapy may be particularly useful for HIV-related therapy in terms of the client-therapist relationship, the focus on observation rather than interpretation, the concept of awareness, and the use of “experiments” and role playing.

Also in the March issue, **Joseph Grebel, PhD,** a therapist in private practice in San Francisco, describes Control-Mastery theory and applies it to HIV prevention.
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