

Psychoneuroimmunology: Can Psychological Interventions Modulate Immunity?

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There is ample evidence from human and animal studies demonstrating the downward modulation of immune function concomitant with a variety of stressors. As a consequence, the possible enhancement of immune function by behavioral strategies has generated considerable interest. Researchers have used a number of diverse strategies to modulate immune function, including relaxation, hypnosis, exercise, classical conditioning, self-disclosure, exposure to a phobic stressor to enhance perceived coping self-efficacy, and cognitive-behavioral interventions, and these interventions have generally produced positive changes. Although it is not yet clear to what extent these positive immunological changes translate into any concrete improvements in relevant aspects of health, that is, alterations in the incidence, severity, or duration of infectious or malignant disease, the preliminary evidence is promising.

Data from a number of studies have shown that various stressors can adversely affect immune function (Ader, Felten, & Cohen, 1991), and the possibility of a reciprocal relationship—the enhancement of immune function through psychological interventions—has generated considerable interest. In this article we briefly review some of the immunological changes that have been associated with stress as well as evidence for the efficacy of various interventions.

One important caveat must be emphasized in the evaluation of psychoneuroimmunology (PNI) intervention studies. If an individual's immune system is functioning satisfactorily, it may not be possible to enhance immune function above normal levels; in fact, it is possible that it would be undesirable to do so. More is not necessarily better; for example, an overactive immune system may lead to autoimmune disease. As an analogy, if one's blood pressure were 110/70, it might be difficult to lower it further through a behavioral intervention, and it is certainly highly questionable whether any concrete health benefits would accrue as a consequence. In the absence of any age, disease, or stress-related downward alterations in a study population's immune function, any intervention designed to enhance immune function could fail to alter immune function because of homeostatic regulation; if effective in enhancing immune function, it could be maladaptive.

This review is limited to peer-reviewed studies. In addition, we excluded studies using secretory immunoglobulin A (IgA) as the sole dependent measure if the researchers did not adequately control for flow rate because of the associated method-

ological problems that make such data uninterpretable (Stone, Cox, Valdimarsdottir, & Neale, 1987).

To measure immune function, blood samples are obtained from subjects, and the numbers or functional abilities, or both, of various subgroups of white blood cells (leukocytes) or their biochemical mediators (e.g., lymphokines) are assayed. There are a number of different leukocyte subpopulations that have specialized functions, and no single assay or group of assays provides a standard, global measure of immune function. However, because the functional activities of leukocyte subpopulations are interdependent, adverse changes in one subgroup can produce multiple cascading effects. In general, qualitative or functional assays appear to be more sensitive to psychosocial stressors than quantitative assays (e.g., see Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991).

Stress-Related Alterations in Immune Function

Stressful events can alter a wide range of immunological activities. For example, even commonplace aversive events such as academic examinations are associated with transient immunological changes. By comparing immunological data collected from medical students during a 3-day examination block in contrast with a baseline or lower stress blood sample collected a month previously, we found significant declines in natural killer (NK) cell activity; these cells are thought to have important antiviral and antitumor functions (Glaser et al., 1987; Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986; Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984). Gamma interferon, a lymphokine that serves as a major regulator of NK cells by stimulating their growth and differentiation, also enhances their ability to destroy target cells (Herberman et al., 1982). In two separate studies, we found dramatic decreases in gamma interferon production by lymphocytes during examinations (Glaser et al., 1986, 1987).

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The large and reliable changes in antibody titers to latent herpesviruses during exams, particularly Epstein-Barr virus (EBV) and herpes simplex Type 1 (HSV-1), are also thought to reflect alterations in the competence of the cellular immune response (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Glaser et al., 1987, 1991). The characteristic elevations in EBV antibody titers during exams are thought to occur in response to the increased synthesis of the virus or virus proteins (Glaser et al., 1991); although counterintuitive, elevated antibody titers to a latent herpesvirus reflect poorer cellular immune system control over virus latency (Henle & Henle, 1982). Consistent with the elevations in herpesvirus antibody titers, specific T-cell killing of EBV-infected target cells decreased during examinations, and a herpesvirus-relevant lymphokine was also altered (Glaser et al., 1987).

The proliferative response of lymphocytes cultured with a mitogen, a substance that stimulates cell replication, is thought to provide a model of the immune system's ability to respond to infectious agents, such as bacteria or viruses. Medical students show a poorer proliferative response to mitogens during examinations, compared with baseline (Glaser, Kiecolt-Glaser, Stout, Tarr, Speicher, & Holliday, 1985).

Interleukin 2 (IL-2) is a lymphokine that is important for T-lymphocyte proliferation, and the IL-2 receptor (the part of the cell to which IL-2 binds) is an important mediator of this response. The percentage of peripheral blood T-lymphocytes expressing the IL-2 receptor was lower during exams compared with lower stress baseline periods in three independent medical student studies (Glaser et al., 1990). Moreover, the level of messenger RNA to the IL-2 receptor in peripheral blood leukocytes decreased during examinations in a subset of these students (Glaser et al., 1990). These are the first data suggesting that stress-associated decrements in immunity may be observed at the level of gene expression.

Examination stress alters phorbol ester inhibition of radiation-induced apoptosis in human peripheral blood leukocytes (PBLs; Tomei, Kiecolt-Glaser, Kennedy, & Glaser, 1990). Apoptosis is the process of genetically programmed alterations in cell structure that leads to the failure of proliferation and differentiation and eventually to cell death. Apoptosis may be induced by a variety of toxic insults, including growth factor deprivation and ionizing radiation, and it is thought to help protect against the appearance of heritable phenotypic changes in cells. These data and others suggest possible connections between stress and carcinogenesis (e.g., Kiecolt-Glaser, Stephens, Lipitz, Speicher, & Glaser, 1985).

The data we have just highlighted demonstrate that even something as transient, predictable, and relatively benign as examination stress modulates a very wide range of immunological activities. Other studies have addressed the question of whether longer-term adaptation occurs when a stressor is more chronic, such as living near a damaged nuclear reactor (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989) or caregiving for a family member with a progressive dementia (Kiecolt-Glaser et al., 1991). The weight of the evidence to date suggests that chronic stressors are associated with continued down-regulation of immune function rather than adaptation.

For example, we assessed changes in immunity and health in 69 spousal dementia caregivers who had already been providing

care for an average of 5 years, and in 69 sociodemographically matched control subjects (Kiecolt-Glaser et al., 1991). During the 13-month interval between the initial sample and the follow-up sample, caregivers showed down-regulation on three measures of cellular immunity relative to controls (decrements in blastogenesis with two mitogens, and increased antibody titers to EBV). The caregivers also reported significantly more days of infectious illness (primarily upper respiratory tract infections) than did controls, as assessed by the Health Review (Jenkins, Kraeger, Rose, & Hurst, 1980), and these data were consistent with physicians' diagnosis.

The evidence from both human and animal studies clearly indicates that stress can down-regulate immune function (Ader et al., 1991). These data have encouraged researchers to explore the possibility that behavioral interventions might have positive consequences for immune function.

Intervention Studies

PNI intervention studies have used a number of diverse strategies, including hypnosis, relaxation, exercise, classical conditioning, self-disclosure, exposure to a phobic stressor to enhance perceived coping self-efficacy, and cognitive-behavioral therapies. Subject or patient populations have included undergraduate and medical students, older adults, cancer patients, men infected with HIV, snake phobics, and normal community volunteers. Outside of the hypnotic work with immediate and delayed hypersensitivity responses, no two studies have used the same methodology or the same immunological measures. Despite this diversity, there are some important common themes suggested by these studies.

Hypnosis and Relaxation

Hypnosis and relaxation have been the most commonly used interventions. Use of the "double arm" technique has provided some of the better controlled hypnotic research. Investigators have used variations of this paradigm with both immediate and delayed hypersensitivity reactions. In these studies, subjects were injected with the same antigen in both arms (e.g., histamine or purified tuberculin protein derivative), and suggestions were made that one arm would show certain characteristic changes (e.g., wheal, erythema, itching, burning, and swelling), whereas the other would not (Black, 1963a, 1963b; Black & Friedman, 1965; Black, Humphrey, & Niven, 1963; Zachariae & Bjerring, 1990; Zachariae, Bjerring, & Arendt-Nielsen, 1989). Although the bulk of the evidence is favorable and differences in responsiveness between arms have been found, there are also negative data (Beahrs, Harris, & Hilgard, 1970), including one well-controlled study (Locke et al., 1987). Moreover, it is not clear whether the observed hypersensitivity changes reflect modulation of immune function or simply surface changes in the skin; in one study, skin biopsies showed reductions in edema without corresponding changes in the degree of cellular infiltration (Black et al., 1963).

Whereas most of the research using hypnosis has focused on immediate or delayed hypersensitivity, one study explored the possibility that a hypnotic/relaxation intervention might have prophylactic value for some aspects of cellular immunity if used

before a stressor (Kiecolt-Glaser et al., 1986). Half of a group of 34 medical students were randomly assigned to a hypnotic/relaxation group that met in the interval between baseline and examination blood draws. NK cell activity and percentages of helper T-lymphocytes declined in both groups during examinations. However, subjects in the hypnotic/relaxation group showed wide variability in their frequency of relaxation practice, ranging from 5 to 50 times. Regression analyses showed that more frequent practice was associated with higher helper T-lymphocyte percentages during examinations after controlling for baseline levels.

Another study assessed the impact of relaxation and social contact with 45 older adults from four independent living facilities (Kiecolt-Glaser, Glaser, et al., 1985). Subjects were randomly assigned to one of three protocols: progressive relaxation training, social contact, or no intervention. Subjects in the relaxation and social contact conditions were seen individually three times a week for a month. Blood samples and self-report data were obtained at baseline, at the end of the 1-month intervention, and at a 1-month follow-up. Only subjects in the relaxation condition produced significant increases in NK cell activity and decreases in HSV antibody titers, both consistent with improved immune function.

A biofeedback-assisted relaxation intervention with medical students during summer vacation produced equivocal results (McGrady et al., in press). Comparisons between relaxation and control subjects showed no differences in their blastogenic response to one mitogen following the intervention, and only one of the two concentrations of another mitogen exhibited the hypothesized Group \times Time interaction. As suggested earlier, stress-reduction interventions may have a minimal impact on immunity in young, healthy, nonstressed populations.

Conditioning

Studies with rodents have provided striking demonstrations of the modulation of immunity, morbidity, and mortality through classical conditioning (e.g., Ader et al., 1991). Although the animal studies are very provocative, conditioning has not been studied as extensively in humans. Smith and McDaniel (1983) altered subjects' delayed hypersensitivity response to tuberculin; those subjects who expected their reactions to a tuberculin skin test to be negative were less reactive after repeated saline injections in the test arm before the tuberculin injection. In another study, women receiving chemotherapy for ovarian cancer developed anticipatory immune suppression, consistent with speculation that patients receiving chemotherapy develop conditioned immune suppression as well as conditioned nausea after repeated pairings of hospital stimuli with the emetic and immunosuppressive effects of chemotherapy (Bovbjerg et al., 1990). Further conditioning studies with humans would be very valuable.

Intervention and Serious Illness: Cancer and AIDS

One obvious area of interest is the possibility of influencing the course of serious illnesses such as cancer or acquired immunodeficiency syndrome (AIDS) through behavioral interventions. Although a number of clinicians have advocated the use

of such techniques as guided imagery for cancer patients (e.g., Gruber, Hall, Hersh, & Dubois, 1988), there are few well-controlled studies. The failure to randomly assign patients to control and intervention conditions is a noteworthy weakness in the cancer arena, making it impossible to assess the effects of any of the treatments. For example, stage of disease can have a profound effect on how patients feel, and cancer treatments such as chemotherapy and radiation are associated with a number of adverse side effects. Without random assignment of patients with the same type and stage of cancer, it is possible that patients who are choosing a treatment are those who are in better health and whose cancer treatments have had fewer adverse consequences.

One of the best studies in this area evaluated both the immediate and longer-term effects of a 6-week structured group intervention that consisted of health education, enhancement of problem-solving skills regarding diagnosis, stress management techniques such as relaxation, and psychological support (Fawzy et al., 1990). The patients had Stage I or II malignant melanoma, and they had not received any treatment after surgical excision of the cancer. The intervention subjects were seen in groups of 7–10 patients who met for 90 min every week for 6 weeks. The researchers found reduced psychological distress and significant immunological changes in the intervention group patients ($n = 35$), compared with the control group ($n = 26$). The former showed significant increases in the percentage of large granular lymphocytes (the NK cell phenotype), an increase in NK cytotoxic activity, and a small decrease in the percentage of helper/inducer T-cells. Most of these changes were not found at the 6-week follow-up but had emerged 6 months later. The majority of the intervention group subjects showed increases on these assays, and the magnitude of these changes was frequently greater than 25%. In contrast, only a third of the control group subjects showed these changes.

A landmark study by Spiegel, Bloom, Kraemer, and Gottheil (1989) showed that a year of weekly supportive group therapy sessions with self-hypnosis for pain extended survival time in women with metastatic breast cancer. The 50 women randomly assigned to the intervention group survived an average of a year and a half longer than the 36 controls, with the divergence in survival beginning 20 months after entry, or 8 months after the intervention had ended; the study included a 10-year follow-up. It is often assumed that these data reflect immunological alterations that influenced the course of the cancer. Although this is one possibility, there are certainly a variety of other interpretations. As Spiegel et al. noted, it is quite possible that subjects in the intervention condition were more compliant with treatment, had better health behaviors such as exercise and diet, or differed on a variety of other health-related behaviors. Such behavioral differences could certainly contribute significantly to the observed outcome. Spiegel and colleagues are in the process of replicating their study, and their protocol now includes immunological measures.

Work with human immunodeficiency virus (HIV) seropositive subjects also appears very promising. An exercise intervention attenuated emotional distress and NK cell decrements following notification of positive serologic HIV status (LaPerriere et al., 1990; LaPerriere, Fletcher, Antoni, Ironson, Klimas, & Schneiderman, 1991). Fifty HIV-seropositive and HIV-seroneg-

ative healthy gay men were randomly assigned to either aerobic training or to a no-intervention control group. Subjects were assessed following the 5-week training period and 72 hours before notification of serostatus, with one further assessment a week after notification. Anxiety and depression increased, and NK cell numbers declined in seropositive control subjects after notification, whereas seropositive exercisers resembled both of the seronegative groups, with no affective or immunological change. Seronegative exercisers also showed a significant net increase in helper/inducer (CD4) cells, whereas seropositive exercisers showed a smaller increase.

In a parallel study from this group, 47 asymptomatic healthy gay men were randomly assigned to either a cognitive-behavioral stress management condition or an assessment-only control group, using the same 5-week period before notification of HIV antibody status as the exercise study (Antoni et al., 1991). The seropositive behavioral intervention subjects showed significant increases in CD4 T-lymphocytes and NK cell counts as well as a slight increment in the mitogen response; as with the exercise study, there were no significant increases in depression after notification in the intervention subjects. In contrast, control subjects showed slight decrements in mitogen responsivity and lymphocyte cell counts from before to after notification. Relative to controls, subjects randomized to either the aerobic exercise or the cognitive-behavioral stress management condition showed decreases in antibody titers to two latent herpesviruses, EBV and Human Herpesvirus Type 6 (Esterling et al., 1990). These investigators noted that they were comparing a comprehensive treatment package with an assessment-only control condition; thus they were not able to parcel out the particular components that may have been most effective. However, there was some suggestion that greater relaxation practice and greater willingness to comply with the intervention were associated with greater change.

In contrast with these positive data, an intensive, well-designed stress-reduction intervention (including relaxation, stress management skills, and health behaviors) did not produce changes in a battery of immunological measures in HIV-seropositive men when compared with waiting-list control subjects at the end of the 8-week intervention (Coates, McKusick, Kuno, & Stites, 1989). The researchers speculated that the group's focus on psychological issues related to AIDS may have simultaneously provoked some anxiety. In addition, there was no manipulation check to assess frequency of relaxation practice, an important point in light of data from other studies (Antoni et al., 1991; Kiecolt-Glaser, Glaser, et al., 1985). Moreover, there was no evidence of affective changes in subjects in the intervention condition, and changes in distress are one of the hypothesized mechanisms underlying the immune changes (Antoni et al., 1991). Subjects in the Coates et al. (1989) experimental group had lower T-cell numbers than the control group, suggesting that they were already more impaired. In addition, there was no HIV-negative control group; an intervention might have affected immune function differentially in healthier seropositive men than seronegative men. Finally, longer follow-up periods are certainly desirable, especially in light of data from Fawzy et al. (1990); as mentioned earlier, they found significant immunological differences between intervention and control subjects at 6 months after the study began, but not at 6 weeks.

It is clear that the immunological underpinnings for HIV and for various cancers are quite different, but both areas offer important arenas for researchers. Even though PNI studies with HIV or cancer populations present their own sets of unique methodological challenges (Kiecolt-Glaser & Glaser, 1988a, 1988b), the possibility of concrete health benefits as demonstrated by Spiegel et al. (1989) is very exciting.

Personal Relationships, Self-Disclosure, and Psychotherapy

The association between personal relationships and immune function is one of the most robust PNI findings. For example, lonelier medical students had poorer immune function than their less lonely contemporaries (Glaser, Kiecolt-Glaser, Speicher, et al., 1985; Kiecolt-Glaser et al., 1984). Medical students who reported greater social support demonstrated a stronger immune response to a hepatitis B vaccine (Glaser, Kiecolt-Glaser, Bonneau, Malarkey, & Hughes, 1992). Marital disruption, either through bereavement or divorce, has been associated with decrements in immune function, and greater marital strife was correlated with poorer immune function in intact marriages (Irwin, Daniels, Smith, Bloom, & Weiner, 1987; Kiecolt-Glaser et al., 1987, 1988; Schleifer, Keller, Camerino, Thornton, & Stein, 1983). Women whose husbands were being treated for urologic cancer, who had higher levels of social support, had better immune function than those who reported less support (Baron, Cutrona, Hicklin, Russell, & Lubaroff, 1990). Among older men and women who were providing care for a spouse with a progressive dementia, those who reported lower social support at intake and who were most distressed by dementia-related behaviors showed the greatest and most uniformly negative changes in immune function at follow-up, 13 months later (Kiecolt-Glaser et al., 1991).

Wiedenfeld et al. (1990) assessed the effects of a perceived self-efficacy intervention with 20 snake phobics. Their intra-subject design generally supported the hypothesis that immune function is modulated by perceived self-efficacy to exercise control over stressors. Although this study is quite provocative, the absence of a control group makes it difficult to interpret these data.

One study explored the tie between self-disclosure and immune function (Pennebaker, Kiecolt-Glaser, & Glaser, 1988). Fifty undergraduates were randomly assigned to one of two groups: Half of the subjects wrote about traumatic or troubling experiences for 20 min on 4 consecutive days, whereas the remainder wrote about trivial events and experiences. The individuals who wrote about traumatic or upsetting events demonstrated a higher mitogen response following baseline, compared with control subjects. Trauma subjects' average number of monthly health center visits dropped following the study, whereas control subjects' visits increased, replicating health data from similar studies (Murray, Lamm, & Carver, 1989; Pennebaker & Beall, 1986). Most important, individuals who wrote about experiences they had not previously shared with other people had a better lymphocyte proliferative response than those subjects who had previously discussed the experiences.

There is solid evidence that use of mental health services is

associated with lower utilization of medical services, including fewer medical visits, fewer days of hospitalization, and lower overall medical costs (Jones & Vischi, 1980; Mumford, Schlesinger, & Glass, 1981). Unfortunately, these studies were not designed to distinguish between physician visits that may be motivated more by distress and those that are related to actual health problems (e.g., Tessler, Mechanic, & Diamond, 1976), and they do not provide specific information on infectious or malignant diseases. Nonetheless, it is certainly possible that interventions, such as psychotherapy, that enhance personal relationships, decrease distress, or enhance perceived self-efficacy could also have positive effects on immunity and, perhaps, health outcomes.

Health Consequences

It is sometimes erroneously assumed that changes in immune function translate directly into changes in health. In fact, whether interventions that produce relatively small immunological changes can actually affect the incidence, severity, or duration of infectious or malignant disease is not known. The answer probably depends on the type and intensity of the intervention, the degree and pervasiveness of immune modulation, and an individual's prior immunological and health status.

Moreover, there are many problems in clearly demonstrating causal relationships. Infectious illnesses occur relatively infrequently in the general population, with most adults reporting only a few illness episodes a year; thus, any decrements in low base rates are extremely difficult to detect, particularly with the relatively small sample sizes necessitated by the time and expense inherent in PNI research. Distressed individuals are more likely to have life-styles that put them at greater risk, including poorer health habits such as a greater propensity for alcohol and drug abuse, poorer sleep, poorer nutrition, less exercise, and so on (Verbrugge, 1979), and these health behaviors affect immunity (Kiecolt-Glaser & Glaser, 1988a). Socially isolated individuals have higher rates of morbidity and mortality (House, Landis, & Umberson, 1988), but presumably they are less likely to have contact with others and thus are less likely to be exposed to pathogens.

An alternative approach to the question of whether interventions can improve health involves weighing the evidence that stress is implicated in infectious illness. Two recent studies provide solid evidence that stress has clear relevance for infectious illness. Cohen, Tyrrell, and Smith (1991) prospectively studied the relationship between stress and susceptibility to colds by inoculating volunteers with one of five different cold viruses or a placebo. They found that rates of both respiratory infection and clinical colds increased in a dose-response manner with increases in psychological stress across all five cold viruses, providing an outstanding, well-controlled demonstration of increased infection associated with increased stress.

Consistent with Cohen et al. (1991), a recent study from our laboratory showed that stress influenced students' response to a viral vaccine. We gave each of a series of three hepatitis B (Hep B) inoculations to 48 medical students on the last day of a 3-day examination series to study the effect of academic stress on the students' ability to generate an immune response to a primary antigen (Glaser et al., 1992). A quarter of the students serocon-

verted (produced an antibody response to the vaccine) after the first injection, and they were significantly less stressed and less anxious than those students who did not seroconvert until after the second injection. In addition, students who reported greater social support demonstrated a stronger immune response to the vaccine at the time of the third inoculation, as measured by antibody titers to a Hep B surface antigen (HBsAg) and the blastogenic response to a viral peptide. We had followed this group of students for a year and a half before this vaccine study, and the earlier and later seroconverters had not differed on anxiety, perceived stress, or social support before the first inoculation.

These data suggest that the immunological response to a vaccine can be modulated by a relatively mild stressor in young, healthy adults, a finding that may have public health implications. Moreover, these data provide a window on the body's response to other pathogens, such as viruses or bacteria. Because the students who were more stressed and more anxious seroconverted later, these same students might also be slower to develop an antibody response to other pathogens; thus, theoretically, they could be at greater risk for more severe illness.

Recommendations for PNI Intervention Studies

Virtually all of the PNI studies with human subjects have been published within the last decade, the majority within the last few years. It is clear that much more is known about the effects of various stressors on the immune system than is known about the consequences of behavioral interventions, particularly the duration of any immunological alterations. The longest follow-up for any intervention study published to date was 6 months (Fawzy et al., 1990); although Spiegel et al. (1989) reported a 10-year follow-up, no immunological data were collected. It seems reasonable to assume that, in general, the narrower the scope of a behavioral intervention and the shorter its time course, the less enduring the benefits, either psychological or immunological.

Many PNI researchers have not collected data on important health behaviors such as sleep, smoking, physical activity, recent weight change, current health status, prescription medications, alcohol or drug use, smoking, caffeine intake, and so on, and these behaviors appear to have immunological consequences (see the more detailed review in Kiecolt-Glaser & Glaser, 1988a). Because many of these behaviors are affected by distress, as discussed earlier, they should be routinely assessed in PNI studies.

Randomization of subjects to treatment and control groups is important, as we pointed out, especially because many of the immunological measures do not have "normal" values. In the ideal study, blood samples would be collected from all experimental and all control subjects at precisely the same time, but this is often an impossibility. When samples are collected on multiple days from different groups of subjects who are hypothesized to differ on some characteristic, it is important that blood samples from the different subject cohorts be run simultaneously (e.g., rather than assaying samples from depressed patients on one day and comparison subjects the next). Schleifer, Keller, Bond, Cohen, and Stein (1989) have shown that there are high correlations because of what they term the *measure-*

ment occasion, the day on which samples are obtained, accounting for as much as 85% of the variance in between-groups differences. To avoid systematic bias, it is important to intermix subjects from various groups when samples are collected.

Distress and poorer personal relationships appear to be associated with the down-regulation of immunity across a number of studies. Psychological or behavioral therapies are often targeted at one or both of these dimensions, and the addition of immunological measures to therapy outcome studies could produce very interesting results. As suggested earlier, the best candidates are probably those individuals who already have some impairments in immune function relative to their age- and sex-matched contemporaries.

In summary, although the number of PNI intervention studies is limited, the results are promising. Further work should provide clearer evidence of the extent to which positive immunological changes may be translated into improvements in health.

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