Questions of Mind Over Immunity

Scientists rethink the link between psychology and immune function

By BRUCE BOWER

Like bacteria multiplying in a moist laboratory culture, investigations of the link between psychological factors and immune function proliferated during the 1980s. Particular interest centered on probes of disturbed immunity among people experiencing either clinical depression or some type of severe stress, such as bereavement.

As data accumulated, a seemingly incurable optimism infected scientists in this relatively new discipline, known as psychoneuroimmunology. Perhaps, they mused, we can show that well-chosen psychological treatments shore up immunity and slow the spread of infectious diseases, from the common cold to virally induced cancers.

But the field with the long name and high hopes now finds itself dealing with a sense of hard-boiled skepticism. Some researchers say studies of stress, depression and immunity contain flaws that render them inconsistent and inconclusive. Others see the data in a better light but acknowledge that depression may have received premature billing as a powerful immunity-buster. And everyone admits that so far no solid evidence connects psychological states to any specific immune disease.

Investigations of stress, depression and immune measures have mainly generated "findings in search of meaning," concludes a team led by psychiatrist Marvin Stein of the Mount Sinai School of Medicine in New York City, writing in the February ARCHIVES OF GENERAL PSYCHIATRY.

In the mid-1980s, Stein's group conducted a study of bereaved men and severely depressed individuals, finding that infection-fighting white blood cells known as lymphocytes displayed stunted proliferation when chemically stimulated to reproduce (SN: 2/16/85, p.100). In a follow-up study, the researchers observed that while younger depressed patients retained normal immune responses, many middle-aged or older depressed patients suffered declines in two types of lymphocytes—helper T-cells and natural killer cells — and in the overall lymphocyte proliferation rate (SN: 5/23/87, p.328). This suggested that depression and immunity dance a complex waltz, not a straightforward two-step.

Depression may simply sit the dance out in cases of HIV infection, according to a report in the February ARCHIVES OF GENERAL PSYCHIATRY. For six months, psychologist Judith G. Rabkin of Columbia University in New York City and her coworkers tracked a group of 124 homosexual men who tested positive for HIV, the immunity-weakening virus that can lead to AIDS. Those enduring the most depression, emotional distress or stressful life events showed no greater drop in the number of helper T-cells and no more advanced symptoms of HIV infection than the others, the researchers found.

Psychiatrist Samuel Perry of Cornell University Medical College in New York City directed a similar HIV investigation last year. Together, Perry's and Rabkin's results suggest that depression and stress "do not have a measurable or substantial effect on the immune system in relation to physical disorders such as AIDS," Stein and his colleagues argue.

Even when a depression-immunity link turns up, its implications prove murky, observe psychiatrist Denis F. Darko of the Veterans Administration Medical Center in San Diego and his colleagues. Among a group of 43 severely depressed men, those with the fewest symptoms of depression displayed lower rates of lymphocyte proliferation than healthy controls, while the most depressed men compared favorably with controls on this lymphocyte measure, Darko's team reports in the March AMERICAN JOURNAL OF PSYCHIATRY. The view that all depressed patients possess stunted lymphocyte function "must be reexamined," they conclude.

Several problems plague psychoneuroimmunology, according to Stein's group. First, the relationship of laboratory measures, such as lymphocyte proliferation and numbers of T-cells and natural killer cells, to actual infection- or tumor-inspired immune responses remains fuzzy. Also, studies of depression and immunity often rely on small samples, lack comparisons with age- and sex-matched controls, and lump depressed patients together regardless of the nature or severity of their mood disorder.

Mounting evidence documents extensive two-way communication between the central nervous system and the immune system, Stein and his coauthors note. Further research may show that depressive disorders somehow participate in the chemical correspondence between brain and immune cells, they contend.

In recent months, Stein has brought his skeptical message to conferences and seminars around the nation. But some other psychoneuroimmunology investigators say Stein takes too dim a view of the data.

"I think Stein undersells this field and what we know, by a lot," says psychologist Janice Kiecolt-Glaser of Ohio State University in Columbus.

"The relation between stress and infectious disease is extraordinarily complex, but Stein views the scientific findings too negatively," says Sheldon Cohen, a psychologist at Carnegie Mellon University in Pittsburgh.

In an extensive review of research on stress and human infectious disease, published in the January PSYCHOLOGICAL BULLETIN, Cohen and Gail M. Williamson,

a psychologist at the University of Georgia in Athens, conclude that stress indeed influences the immune system, but they note that scientists have yet to uncover any evidence pinning stress-induced dips in immune function to the appearance of a specific disease.

Several studies in the past 30 years have indicated that people experiencing stressful life events or considerable family distress report more symptoms of upper respiratory infections, such as colds and influenza, and visit physicians more often because of these health problems, Cohen and Williamson point out. But such findings, they say, may largely reflect stressed individuals' increased sensitivity to minor disease symptoms or their tendency to seek solace from medical care.

A growing body of evidence also suggests that stress may reactivate herpesviruses, possibly reigniting infectious disease, the two researchers say. Herpesviruses cause a range of reactions – from genital and "cold" sores to mononucleosis – and often remain dormant in the body after symptoms disappear.

Much of the work in this area comes from the laboratory of Kiecolt-Glaser and her Ohio State colleague, psychologist Ronald Glaser. In the last six years, they have reported increased production of antibodies against several herpesviruses not only among medical students about to take exams, but also among women recently separated from their husbands, men who are separated or divorced, and caregivers of patients with Alzheimer's disease.

In a new report, to appear later this year in PSYCHOSOMATIC MEDICINE, the Ohio State team details significant deterioration in three aspects of immune function over a 13-month period among people who care for spouses with Alzheimer's disease while receiving poor "social support" – a measure of the number and quality of an individual's important personal relationships. The researchers probed immune function with two substances that stimulate lymphocyte proliferation. They also checked for the presence of antibodies to a herpesvirus known as Epstein-Barr virus.

Social support bore no relation to sheer numbers of lymphocytes or natural killer cells, they found. Measures of immune-cell function, in this case lymphocyte proliferation and antibody reactions, appear more sensitive to disturbance by psychological factors, Kiecolt-Glaser says.

Although the 69 men and women caring for a demented spouse reported more depression than 69 controls not involved in caregiving activities, depressed participants retained normal immune function, the researchers report.

An unpublished study directed by Ronald Glaser indicates that people with poor social support also exhibit delays in immune response to hepatitis vaccine, suggesting that their bodies may struggle to process many commonly used vaccines. Glaser's team gave 48 medical students a hepatitis vaccine injection, followed by another injection one month later and a booster shot five months after that. In blood tests performed at the time of the second vaccination, students reporting the least social support showed significantly fewer antibody-generating hepatitis antigens than the rest of the study group. In addition, their lymphocytes responded sluggishly when exposed to the hepatitis antigen. Depression appeared to have no independent impact on immune responses.

By the time they received the booster shot, all students had developed adequate hepatitis antibodies.

"Several years ago, I thought depression was linked to lower immune function," Kiecolt-Glaser says. "Now it looks like I was wrong. Social support seems more important in relation to immunity."

Psychiatrist Karl Goodkin agrees. Among psychologically healthy individuals with a compromised immune system, such as those infected with HIV, social support combines with two other psychological factors – stressful events and the person's style of coping with stress – to influence immune function, Goodkin says.

Data on stressful occurrences during the previous year, such as moving or undergoing a divorce, usually come from a patient's self-reports. Coping style in response to stress generally breaks down into two categories: passive coping, marked by resignation; and active coping, involving some sort of coordinated response to a threat.

In a pilot study of 11 homosexual men infected with HIV but showing no AIDS symptoms, Goodkin and his colleagues at the University of Miami found that the men with active coping styles and low levels of life stress possessed the most helper T-cells. Active copers under high stress and passive copers under minimal stress displayed slightly lower numbers of helper T-cells. Passive copers under high stress had the fewest such cells. The researchers reported their findings in January 1990 at the annual meeting of the American Association for the Advancement of Science, held in San Francisco.

Goodkin's team statistically controlled for a variety of other factors that affect immunity: sleep disturbances, prescription drug use, exercise level, diet, alcohol consumption, caffeine consumption and cigarette smoking. Goodkin suggests that the stability of helper T-cell counts among depressed HIV-positive men in Rabkin's study may reflect the absence of such controls.

In addition, HIV may so overwhelm the immune system in the first few years following infection that it blocks out any psychological influences on immunity, Kiecolt-Glaser maintains.

However, in a pilot study directed by psychologist Mary Ann Fletcher of the University of Miami, newly diagnosed HIV-positive men who participated in a 10-week aerobic exercise group displayed moderate but statistically significant increases in helper T-cells (SN: 8/20/88, p.116). The seven men also reported less anxiety, depression and confusion than seven HIV-positive men not taking part in the exercise group. Besides increasing physical stamina, group aerobics also promotes better social support and active coping, Fletcher says.

The future of such investigations may depend on a better understanding of individual differences in immune-system sensitivity to stress, Cohen maintains. In the March PSYCHOLOGICAL SCIENCE, Cohen and others report that the sympathetic nervous system, orchestrator of the body's response to stress, appears to mediate immune reactions to psychological challenge.

That study, led by psychologist Stephen B. Manuck of the University of Pittsburgh, began with a frustrating, 20-minute laboratory task involving the rapid presentation of a word test and mental arithmetic problems. Immediately after taking the test, the nine men whose sympathetic nervous systems became highly activated – as reflected by elevated heart rates, blood pressure and adrenaline levels during the task – also displayed a stunted rate of lymphocyte proliferation and greater numbers of suppressor T-cells, which inhibit immune function. But the 11 men with low activation of the sympathetic nervous system underwent no immune changes.

"It's hard to judge the significance of immune effects in these types of studies, since immunologists haven't studied changes in immunity among healthy people too closely," Cohen acknowledges.

Despite the problems inherent in this research, Cohen expects further work to uncover a clear link between depression and lowered immunity. He notes that severe depression causes the release of several hormones that modulate immune function, and usually involves immunity-undermining behaviors such as lack of sleep, poor nutrition and increased use of alcohol and cigarettes.

Part of the new skepticism toward psychoneuroimmunology, Goodkin adds, stems from popular accounts and best-selling books that improperly cite these studies as proof that the "right attitude" cures all sorts of serious diseases.

"The lay public often responds to this data with overexuberance," Goodkin says. "The medical community tends to respond with a lot of cynicism. I hope we can find some middle ground." □