Behavioral Influences on Immune Function: Evidence for the Interplay between Stress and Health

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Within the voluminous life events literature, the objective evidence for a causal relationship between stressful events and organic disease has not been impressive. Correlations between life change scores and self-reported health are typically in the .30s or lower (Thoits, 1983). In the great majority of life events studies, researchers have found that only a minority of individuals actually show organic disease when objective assessment procedures are used.

In this chapter we discuss immunologic evidence supporting a causal relationship between major and minor stressful life events and infectious disease in humans. We present data suggesting that the increased distress regularly linked with life events is also associated with poorer immune function. Based on these data, we argue that while declines in immune function are a very frequent concomitant of even certain commonplace life events, factors such as the prior health of the individual (particularly in regard to immune system function) and recent exposure to pathogens are important in determining the actual organic disease outcomes. In addition, we suggest that psychological resources which reduce distress (e.g., supportive interpersonal relationships) also concurrently attenuate adverse immunological changes.

We focus on psychoneuroimmunologic research with humans. The interested reader may wish to consult Borysenko and Borysenko (1982), Riley (1981), Monjan (1981), or Fox and Newberry (1984) for more information on related research with rodents.

BACKGROUND INFORMATION: IMMUNE SYSTEM

The immune system is the body’s defense against infectious and malignant disease. In order to measure immune function, blood is obtained. and the num-
bers and/or functional abilities of subgroups of white blood cells (leukocytes) are assayed.

There are a number of subpopulations of leukocytes which perform specialized immunologic functions. There is no single immunological assay which provides a global measure of immune system function. However, because of the interdependence of the various components of the immune system, adverse changes in one subpopulation of lymphoid cells are likely to produce multiple effects. Table 9.1 provides brief definitions for the major immunological terms used in this chapter.

The time course for immunological changes should be kept in mind. Unlike hormonal changes which can occur within the course of an hour, many components of the immune system take days or even weeks to change significantly, because of the preexisting numbers and types of cells, as well as the time involved in cell replication. Although certain biochemical mediators may be rapidly synthesized in hours, significant changes in most lymphocyte subpopulations seem to take considerably longer.

There appear to be multiple pathways through which the central nervous system and the immune system can communicate. It is well known that hormones are very responsive to at least certain emotional states, and there is good evidence for endocrine and neuroendocrine mediation of immune function (Ahlgvist, 1981; Blalock, 1984). In addition, there may be direct connections as well; e.g., hypothalamic lesions can produce immunologic changes (Stein, Schleifer, & Keller 1981).

**LIFE EVENTS, DISTRESS, AND IMMUNE FUNCTION**

Earlier human psychoneuroimmunological research focused on the effects of very novel and very intense events on the immune response. Researchers used very small subject samples to demonstrate decrements in lymphocyte proliferation following mitogen stimulation in response to such events as the space flights of astronauts (Kimzey, 1975), bereavement following the death of a spouse (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977), or exposure to 48 or 77 hours of sleep deprivation, noise, and stressful experimental tasks (Palmblad, 1981).

In contrast, the primary focus of work from our laboratory has been on the effects of relatively commonplace events on immune function. We reasoned that if stress-related immunosuppression were indeed a risk factor of any importance in the incidence of infectious disease (and perhaps malignant disease as well), then there should be significant immunological changes associated with more commonplace stressful events, as well as intense and novel events.

In our first study blood was drawn twice from 75 first-year medical students (Kiecolt-Glaser, Garner et al., 1984). The first blood draw occurred 1 month
before final examinations, and the second occurred on the 1st day of final examinations. We found a significant decrease in natural killer cell (NK) activity in the examination sample. In addition, lonelier students (those who scored above the median on a loneliness scale) had significantly lower levels of NK activity. These data suggest that an important host defense may be adversely affected by a commonplace stressful event; there may be implications for health, because of the antitumor and antiviral functions of NK activity. NK cells appear to be critical in the prevention of tumor growth and metastasis in animal models (Herberman et al., 1982).

We found a similar association between higher levels of loneliness and poorer immune function using newly admitted, nonmedicated, nonpsychotic psychiatric inpatients (Kiecolt-Glaser, Ricker et al., 1984). The lonelier psychiatric patients had significantly lower levels of NK activity, as well as a poorer T-lymphocyte response to mitogen stimulation.

We found further evidence for the psychosocial modulation of NK cells in another study using 40 second-year medical student subjects. Three different NK cell assays showed significant decrements during examinations, in comparison to baseline samples taken earlier: (1) lysis of MOLT-4 cells (a different NK target cell than we had used in our previous studies), (2) percentage of NK cells as assessed by the monoclonal antibody anti-Leu-7; and (3) percentage of large granular lymphocytes, the NK cell phenotype. There was also a large change in the production of interferons by lymphocytes stimulated with a mitogen, dropping from a baseline mean of 2003.0 U/ml to 80.00 U/ml during examinations (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986b).

The large changes in interferon production may be related to the NK cell changes, since interferon is a major regulator of NK activity. Interferon can affect the growth and differentiation of NK cells from their progenitor cells. Interferon can also activate the lytic properties of target-binding cells, enhance cytolysis of target cells, and increase the number of target cells which can be killed by an effector cell (Herberman et al., 1982).

We have found reliable decrements in a number of facets of cellular immune function during examinations. We have also found significant stress-associated increases in plasma immunoglobulins in two different medical student classes, with all values in normal range (Glaser et al., 1986a; Kiecolt-Glaser, Garner et al., 1984). These data should be considered, however, in the context of the patterns of immune function in certain kinds of immunosuppressed patients, such as those with AIDS: In such patients, hypergammaglobulinemia (increased immunoglobulin production) is simultaneously associated with deficits in cellular immune function (e.g., Pitchenik, Fischl, & Spira, 1983). While AIDS patients certainly manifest much larger and more severe changes in immune function than the medical students, it is possible that there are common mechanisms underlying different types of immunosuppression which produce parallel changes in immune function.

**PSYCHOSOCIAL INFLUENCES ON HERPESVIRUS LATENCY**

There are convergent animal and human data which implicate stress or distress as a risk factor in the development of primary herpesvirus infections, the duration of the acute episode or primary lesion, and the frequency with which subsequent lesions (herpes simplex types 1 and 2) reappear after the primary lesion. Immunological data provide a much more sensitive way to examine changes in virus latency, in contrast to simply assessing the presence or absence of lesions or other symptoms, since the clinical symptoms are mediated through changes in cellular immune function.

There are five human herpesviruses, as listed and described in Table 9.1. Once infected with any of the herpesviruses, the host will remain latently infected with that particular herpesvirus for life; unlike other viruses such as measles, the herpesviruses are able to escape destruction by the immune system in ways which are not well understood (Glaser & Gotlieb-Stematsky, 1982). When cellular immune system function is compromised (e.g., in patients with immunosuppressive diseases such as AIDS, or in patients undergoing immunosuppressive therapies), immunological control over the latent herpesviruses is impaired, and there are characteristic elevated herpesvirus antibody titers. These elevated antibody titers are thought to reflect an enhanced humoral immune system response to increased virus replication. Improvements in cellular immune system function (e.g., following cessation of immunosuppressive therapy) are followed by decrements in antibody titers.

In previous research, West Point cadets who were seronegative for EBV (i.e., not previously infected) on entry into the military academy were followed for 4 years (Kasl, Evans, & Niederman, 1979). Those who had a triad of psychosocial risk factors (high levels of motivation, poorer academic performance, and having a father who was an "overachiever") appeared to have an increased risk for EBV infection. In addition, both elevated antibody titers among individuals who seroconverted without apparent clinical symptoms and the length of hospitalization among those with clinical symptoms were also significantly related to the risk factor triad.

The frequency of HSV-1 and HSV-2 lesions also appears to be related to psychological distress. Nonpsychotic psychiatric illness has been associated with a greater recurrence rate of genital herpes lesions (Goldmeier & Johnson, 1982). Among student nurses, general unhappiness was predictive of the frequency of cold sores (Luborsky, Mintz, Brightman, & Katcher, 1976).

Using a prospective design, we assessed changes in antibody titers to three latent herpesviruses (EBV, CMV, and HSV) in medical students (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985a). Three blood samples were obtained from 49 first-year medical students, with the first sample drawn 1 month before final examinations, the second on the 1st day of final examinations, and
the third during the 1st week after their return from summer vacation. There were significant changes in the antibody titers to all three herpesviruses across the sample points, with the lowest levels found in the third sample, where students also reported the least distress. In addition, lonelier students had significantly higher antibody titers to two different EBV antigens in contrast to their classmates who described themselves as less lonely.

The changes in antibody titers for EBV and HSV were quite large. For example, the geometric mean EBV antibody titers to virus capsid antigen were over 640 at the first two sample points, declining to 93 after summer vacation. These data are particularly noteworthy, in that seroepidemiological studies have suggested that the geometric mean titer in the adult population is about 80 (Henle & Henle, 1982). We have also found significant changes in the transformation of B-lymphocytes by EBV during examinations (Kiecolt-Glaser, Speicher, Holliday, & Glaser, 1984).

Distress-related changes in the immune system’s control of latent herpesviruses may have associated risks. The herpesviruses are multipotential, having the ability to produce multiple kinds of disease (Glaser & Gotlieb-Stematsky, 1982). For example, while HSV-1 is most frequently associated with the induction of cold sores, it can also produce generalized infections, encephalitis, and death (Adam, 1982). Similarly, the mononucleosis symptoms characteristic of primary CMV infections in individuals with a normal cellular immune response are generally resolved in 3 to 6 weeks (Sullivan & Hanshaw, 1982). However, immunosuppressed patients have high rates of morbidity and mortality associated with both the primary infection and infections resulting from reactivation of endogenous latent virus: The single major known cause of interstitial pneumonia in patients receiving immunosuppressive therapy for bone marrow transplants is CMV.

**RELAXATION AND HYPNOSIS**

Based on our studies with medical students and psychiatric inpatients, we reasoned that interventions that reduced distress and/or loneliness might lead to an enhancement of immune function. We recruited subjects from local geriatric independent living facilities because previous research with institutionalized older adults indicated that increased attention reliably produced small but consistent positive effects (Schulz, 1980). Brief interventions (e.g., college student visits) have been associated with significant improvements in residents’ moods, activity levels, memory, and self- and physician-rated health (Rodin, 1980; Schulz, 1980).

Our 45 geriatric subjects were randomly assigned to one of three protocols: progressive relaxation training, social contact, or no intervention. Subjects in the relaxation training and social contact conditions were seen individually 3 times a week for a month; they were visited by the same student each time. Blood
samples and self-report data were collected at baseline before the intervention began, at the end of the 1-month intervention, and at a 1-month follow-up (Kiecolt-Glaser et al., 1985a).

At the end of the intervention, the relaxation group had significantly higher levels of NK cell activity than at baseline, and significantly lower levels of antibody to HSV and self-rated distress. While NK cell activity and self-related distress were not significantly different from baseline levels in the relaxation group at follow-up, antibody to HSV was still significantly lower than at baseline. There were not significant changes on these variables in either the social contact or no intervention groups. However, there was a general increase across groups at the end of the intervention in the T-lymphocyte response to PHA stimulation, with greater change at lower mitogen concentrations.

These data suggest that psychosocial interventions may significantly enhance immune function. These data have particular relevance for the elderly, because significant decrements in immune function are associated with aging (Braveman, in press). Poorer cellular immune function is associated with greater mortality in individuals over 80-years-of-age (Roberts-Thomson, Whittingham, Youngchaiyud, & MacKay, 1974).

These data may also have implications for possible interventions that might contribute to the control of herpesvirus latency. Consistent with the stress-related changes in our medical student herpesvirus antibody data, the geriatric relaxation subjects' decrements in HSV antibody titer suggest that common clinical stress-reduction interventions might have positive effects on immune function and herpesvirus latency.

We conducted a different kind of intervention study with first-year medical students (Kiecolt-Glaser et al., 1986). The first blood sample was obtained 1 month before the second block of examinations, and the second blood sample was obtained on the last day of the 3-day examination period. We measured changes in the percentages of helper and suppressor T-lymphocytes because of their important immunological functions: helper cells stimulate the activities of a number of other immunologic cells, e.g., helper cells stimulate B-lymphocytes to produce antibody. Large reductions in the relative percentage of helper cells can produce immunodeficiency (Reinherz & Schlossman, 1980). Suppressor cells act in a feedback loop to shut off the activities of helper cells following sufficient action of the helper cells. NK activity was also assessed, as before.

In order to further examine the effects of relaxation, half of the medical students were randomly assigned to a hypnotic/relaxation group which met in the interval between blood draws. Across both groups there was a significant decrease in the percentage of helper T-lymphocytes; NK activity declined significantly as well. Frequency of relaxation practice was a significant predictor of the percentage of helper cells in the examination sample, but did not significantly predict either the percentage of suppressor cells, or NK activity.

We also assessed changes in nutritional status using three biochemical nutritional assays, transferrin, total iron binding protein, and albumin. We included these assays to explore the possibility that the changes in immune function across studies might simply reflect underlying changes in nutritional status: there are well-documented impairments in various aspects of immune function in undernourished individuals, and moderate to severe protein-caloric malnutrition is associated with increased frequency and severity of infection (Chandra & Newberne, 1977). The three plasma protein markers were well within normal limits at both sample points.

There are also other kinds of intervention studies using immunological measures. Consistent with demonstrations by Ader and Cohen (1982) on the classical conditioning of certain aspects of immune function, recent data suggest possible conditioning of the delayed hypersensitivity (allergic) response in humans. Subjects were less reactive to a tuberculin skin test when they expected their reactions to be negative, following previous injections of saline in the test arm (Smith & McDaniel, 1983).

Hypnotic research using the "double arm" technique also suggests possible psychological mediation of delayed hypersensitivity reactions. Subjects with a known allergic response to a particular substance were injected with equal amounts in both arms, and suggestions were made that one arm would show changes, but not the other. Convergent data across different laboratories suggest that such effects are replicable, but may be a function in part of the hypnotic responsiveness of the subject (Beahrs, Harris, & Hilgard, 1970; Black, 1969; Good, 1981).

Related research with 18 asthmatic patients compared the size of skin test responses to allergens following hypnotic suggestions of no responsiveness with the skin test responses of randomly assigned control patients who were not given any suggestions (Fry, Mason, & Pearson, 1964). The patients in the hypnotic suggestion group had significantly smaller wheals than the control patients. In a second study, 29 asthmatic patients were randomly assigned to one of three conditions: (1) hypnotic suggestions that the right arm would not react to skin tests, (2) hypnotic suggestions that both arms would be nonreactive, or (3) hypnotism without suggestions for change. While there were no differences among the treatment groups, all had significantly smaller wheals compared to their baseline measures.

**DEPRESSION AND IMMUNE FUNCTION**

We have found reliable decrements in a number of facets of immune function in otherwise healthy medical students during examinations. Other investigators have taken a different approach, comparing immunologic data from depressed patients and nondepressed controls. Not surprisingly, the depressed patients in these studies have significantly poorer immunologic function, across a number of assays. For example, depressed patients have significantly lower percentages of helper T-lymphocytes (Krueger, Levy, Cathcart, Fox, & Black, 1984), and a
significantly poorer response to mitogen stimulation (Schliefer et al., 1984) than their nondepressed matched counterparts. The number of peripheral T-lymphocytes was also significantly lower among depressed patients than in matched controls (Schliefer, Keller, Siris, Davis, & Stein, 1985). The degree of immunological impairment with a psychiatric population may be related to the severity of depression (Schliefer et al., 1985).

There are also studies with psychiatric patients which have compared herpesvirus antibody titers in patients to those of controls. Certain psychiatric patient subgroups, particularly those who are more depressed, have significantly higher herpesvirus antibody titers than nonpsychiatric controls; no differences between the patient and control groups have been found when other viral antigens such as measles or rubella were used (e.g., Halonen, Rimom, Arokonka, & Jantti, 1974; Lycke Norby, & Roos, 1974). Therefore, some of the researchers have suggested that the herpesviruses may have an etiologic role in certain psychiatric disorders. The previously discussed stress-related changes in antibody to HSV, CMV, and EBV in the medical student data (Glaser et al., 1985a) suggest that a more parsimonious explanation may be related to the higher levels of distress which are characteristic of certain psychiatric diagnoses.

CARCINOGENESIS

Exposure to environmental carcinogens occurs daily. Some carcinogens occur "naturally," e.g., aflatoxin is the carcinogenic product of a mold associated with peanuts and certain grains, while the benzopyrenes, another group of chemical carcinogens, are found in smoke and soot. There are also a growing number of carcinogens of human manufacture: Fruits and vegetables may have pesticide residues, while nitrates are found in many processed meats and some American beers.

Most carcinogens appear to induce cancer by damaging the DNA in cells (Setlow, 1978). Mutant cells formed in this way may develop and proliferate. However, most DNA changes are probably not cancerous, and most carcinogen exposure is limited.

In addition, the body has a hierarchy of mechanisms for dealing with carcinogen exposure. At the first level, there are enzymes which destroy chemical carcinogens. The second stage of defense involves the repair of damaged DNA molecules after carcinogen exposure. At the third level is the immune system's destruction of mutant cells; NK activity is thought to be of primary importance in this regard.

The second level of the hierarchy, the mechanisms for repairing damaged DNA, may be the most critical step in humans. There is excellent evidence that poorer repair of damaged DNA is associated with increased carcinogenesis; for example, individuals with xeroderma pigmentosum (XP) have a genetically based deficit in their ability to repair DNA damaged by the ultraviolet radiation in sunlight. These XP individuals also have significantly greater numbers of skin cancers than individuals without the defect. Even minor defects in the DNA repair system can result in a significantly increased incidence of cancer (Setlow, 1978).

We were interested in ascertaining whether very high levels of distress might be associated with any deficits in the DNA repair process. In order to maximize distress in our initial subject sample, we used 28 nonpsychotic, nonmedicated new psychiatric admissions. Blood samples were drawn and the MMPI was administered on the 1st week day after their admission. Subjects were divided into high- and low-distress groups using a median split on MMPI scale 2 (depression). The T-score mean of the high-distress group was 91.3, while the mean of the low-distress group was 67.5. Comparisons between the two groups on age, sex, alcohol intake, weight loss, smoking intensity and duration, number of previous admissions, psychiatric diagnosis, and presence of a sleep disturbance did not reveal even marginal differences between the groups.

We measured the repair of DNA in lymphocytes exposed to 100 rads of X-irradiation. The method used to measure DNA repair involved the assessment of changes in the three-dimensional structure of the DNA molecule by measuring the distance traveled in a gradient when centrifuged at very high speeds. This technique is particularly sensitive to alterations such as DNA strand breaks, which decrease the migration rate in the gradient. Each subject's data were computed by dividing their irradiated values by their nonirradiated values at 0, 2, and 5 hours after irradiation; using this formula, values less than 100% indicate incomplete repair.

The high-distress inpatients had significantly poorer repair than the low-distress group; most importantly, while most "normals" are fully repaired at the 5-hour endpoint using this assay, the high-distress group was only repaired to 85% of baseline values. Further comparisons between the group of psychiatric inpatients and age- and sex-matched Red Cross blood donors showed significantly poorer DNA repair in the former at the 5-hour endpoint (Kiecolt-Glaser, Stephens et al., 1985b).

These DNA data implicate distress as a possible risk factor for poorer DNA repair, and thus potentially for carcinogenesis. However, the cross-sectional nature of this study does not permit the exclusion of viable alternative hypotheses, e.g., there could be a common genetic determinant for certain kinds of affective disorders and poorer DNA repair. Therefore, we designed a second study to test the hypothesis that stress would induce defects in one facet of the DNA repair system.

Forty-four rats were given the carcinogen dimethylnitrosamine in their drinking water. The carcinogen induces methyltransferase, a DNA repair enzyme, in response to carcinogen damage. Half of the animals were subjected to periodic rotational stress for 16 days (Riley, 1981), and then all rats were sacrificed. We
found significantly lower levels of methyltransferase in cells obtained from the spleens of the stressed animals, suggesting that stress may play a causal role in carcinogenesis (Glaser, Thorn, Tarr, Kiecolt-Glaser, & D’Ambrosio, 1985b).

The inpatient and rat DNA repair data both suggest that distress may have adverse effects on DNA repair. Coupled with the evidence that NK activity is adversely affected by stressors, these data provide evidence for both direct and indirect biochemical pathways through which distress could influence the incidence of cancer.

### DISTRESS, MORBIDITY, AND MORTALITY

The significant immunologic decrements found across several medical student classes are particularly noteworthy when considered in the context of the students' previous exposure to examinations. The selection of students for medical school is based largely on their previous performance on academic examinations. Despite their repeated exposure to this very situation, they still show significant and reliable immunologic decrements.

We suggest that the distress associated with examinations is comparable to that evoked by other commonplace events. For example, the days immediately preceding departure on vacation frequently have a similar affective quality, with comparable time pressures, as work which would normally be done in the following days or weeks is compressed into a much briefer time interval. Similarly, several days spent in the company of certain of one's relatives or in-laws can evoke characteristic negative emotional responses. If the quality and intensity of emotional distress in these and similar situations is similar to that experienced by the medical students, then there may well be similar immunologic changes.

In research to date from our laboratory and others, stress-related depressions in immune function have not been clearly associated with health problems, with one exception (Cohen-Cole et al., 1983). However, there are certainly studies in the immunological literature linking impaired immune function and health (Chandra & Newberne, 1977). The absence of concurrent health impairments in the sparse human psychoimmunology literature to date may reflect the transient nature of the stressors used, the limited time periods subjects have been studied, and/or the degree to which subjects pay attention to health problems when other events such as examinations are more salient.

It is also possible that the chronicity of the stressor is an important factor. In contrast to the data showing the immunosuppressive effects of acute stress, data from one rodent study by Monjan and Collector (1977) suggest that more chronic stress may lead to an enhancement in immune function. Using daily high intensity intermittent noise, they showed that while the acute or short-term consequence of the auditory stressor was immunosuppression, more chronic exposure resulted in enhanced mitogen responsiveness. Similarly, Sklar and Anisman (1979) found that tumor size and survival were adversely affected by a single session of inescapable shock in mice injected with a tumor. Mice which underwent 10 daily shock sessions had tumor areas which were significantly less than that of controls, and survival times which approximated those of controls.

It should be noted, however, that Monjan and Collector (1977) operationalized "chronicity" as the changes which occurred over a 45-day period, with the enhancement in mitogen responsiveness (values above baseline levels) beginning between days 10 and 20. These rodent data should be contrasted with some of the available human data. For example, the DSM-III diagnostic criteria for major depression, the diagnostic category most frequently studied to date, specifies that the essential symptoms must have been present for a period of at least 2 weeks; in fact, most of the patients with a major depression diagnosis in our setting retrospectively report the presence of the salient depressive symptoms for weeks or months before entry into treatment. If there were simply parallel changes between rodents and humans in response to a chronic stressor, then we might reasonably expect the depressed patients to show enhanced mitogen responsiveness, rather than the previously documented decrements (Schliefer et al., 1984).

If stress-related impairments in immune function result in poorer host resistance, then epidemiological studies should show an association between distress and morbidity and mortality, particularly with respect to infectious disease. In fact, there are epidemiological data supporting the association. For example, Babigian and Odoroff (1969) found that psychiatric patients had mortality rates one and one-half to two times as high as those for the general population, even after removal of the high-risk aged, chronically ill, and alcoholic subpopulations. Divorced individuals have a significantly greater incidence of depression than married controls, and also have significantly more deaths due to pneumonia and tuberculosis, as well as a greater variety of nonimmunologically mediated causes such as accidents (Bloom, Asher, & White, 1978). Bereaved spouses have significantly greater rates of morbidity and mortality than their nonbereaved counterparts (Ernst, Sacks, Selvin, & Petakis, 1979; Rees & Lutkins, 1967).

There are also epidemiological data which link distress and cancer risk. Using a sample of over 2000 nonpsychiatric men, Shekelle et al. (1981) compared those subjects whose highest score on the MMPI was scale 2 (depression) with men who did not have scale 2 as their high point code. They found that the men with their highest elevations on scale 2 (T-score mean of 70) had twice the number of cancer deaths, across cancer sites, after correction for a number of relevant risk factors; these data are consistent with our DNA data (Kiecolt-Glaser, Stephenson et al., 1985b). Furthermore, psychiatric patients have more cancer deaths than nonpsychiatric controls (Fox, 1978b). Bereaved spouses have a greater mortality rate from cancer than the general population (Ernst, Sacks, Selvin, & Petakis, 1979).

There are several reasons why the hypothesized association between distress and cancer risk may not be obvious in prospective epidemiological research. The time period for the study is one critical factor. Fox (1978a) presents the mathe-
matical basis for the doubling time of cells, and concludes that a solid tumor would not be visible until at least 3 years after the initial proliferation of a mutant cell; the developmental time span could cover decades, with a mutation held in check for some time. Most studies addressing psychosocial factors have used relatively short time periods.

In addition, distress is not constant, especially at the very high levels which were associated with impairments in DNA repair in our psychiatric patients. Most studies simply assess distress at a single point in time.

Finally, and most important, there are a number of other risk factors which may be much more salient. Carcinogen dosage and period of carcinogen exposure are certainly of paramount importance. Genetic vulnerabilities for certain cancers are also well-documented. There are also newer data which suggest that there may be some important genetic differences in immunocompetence as well; individuals from cancer-prone families have lower levels of NK activity (Strayer, Carter, Mayberry, Pequignot, & Brodsky, 1984).

THE FUTURE OF PSYCHONEUROIMMUNOLOGY RESEARCH

There is still relatively little human research which addresses the psychological mediation of immune function. Although such research is widely accepted by behavioral scientists, it has not achieved comparable acceptance in the basic science community among immunologists and related disciplines, and basic scientists are the essential collaborators for this interdisciplinary work. Some of this lack of acceptance may be related to earlier learning; as recently as the late 1970s, there were still immunology textbooks being published which stated there was no central nervous system mediation of immune function (Ader, 1980). Most of the newer immunology textbooks still do not explicitly address the evidence for the multiple central nervous system and immune system linkages.

In some cases it appears that the importance of the work has not been adequately evaluated. For example, the editor of Nature recently printed an editorial inauspiciously titled “Psychoimmunology: Before its time” (Maddox, 1984). The editorial grossly misrepresented the status of research and theory in the area, describing unreferenced psychoimmunologists “who talk as if there is no state of mind which is not faithfully reflected by a state of the immune system” (p. 400).

Despite such adverse events, there are growing numbers of biological and behavioral scientists who are initiating research in this area (Marks, 1985). Ultimately, psychoneuroimmunological research may change the ways in which biological scientists conceptualize some of the processes they are studying, as well as their data collection procedures.

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