Published in final edited form as:
Am Psychol. 1994 May ; 49(5): 389–404.

A Biobehavioral Model of Cancer Stress and Disease Course

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Abstract

Approximately 1 million Americans are diagnosed with cancer each year and must cope with the disease and treatments. Many studies have documented the deteriorations in quality of life that occur. These data suggest that the adjustment process is burdensome and lengthy. There is ample evidence showing that adults experiencing other long-term stressors experience not only high rates of adjustment difficulties (e.g., syndromal depression) but important biologic effects, such as persistent downregulation of elements of the immune system, and adverse health outcomes, such as higher rates of respiratory tract infections. Thus, deteriorations in quality of life with cancer are underscored if they have implications for biological processes, such as the immune system, relating to disease progression and spread. Considering these and other data, a biobehavioral model of adjustment to the stresses of cancer is offered, and mechanisms by which psychological and behavioral responses may influence biological processes and, perhaps, health outcomes are proposed. Finally, strategies for testing the model via experiments testing psychological interventions are offered.

Cancer is a major health problem, accounting for 23% of all deaths in the United States. Although death rates from heart diseases, stroke, and other conditions have been decreasing, deaths due to cancer have risen 20% in the past 30 years (American Cancer Society [ACS], 1993). This “big picture” holds for the major sites of disease, including lung, breast, and prostate cancer, for which death rates have shown large increases. The number-one killer, lung cancer, has shown huge increases in age-adjusted death rates in the past 30 years—an increase of 121% for men and 415% for women. The second most common site of cancer for men, prostate, has shown a 12% increase in the death rate. For women, breast cancer accounts for 32% of all new cases. During this decade alone, more than 1.5 million women (1 in 9) will be diagnosed and 30% of these women will die from the disease. Other sobering statistics indicate that since 1980 there has been a 24% increase in breast cancer incidence; despite major clinical studies (including trials of dramatic treatments, e.g., bone marrow transplantation), breast cancer mortality rates have been stable for the past 20 years. In sum, increasing numbers of individuals are being diagnosed, undergo difficult therapies, and somehow cope with 5-year relative survival rates of 53% for White Americans and 38% for Black Americans (ACS, 1993).

Although there are notable exceptions (e.g., Bard & Sutherland, 1952; Fox, 1976), research programs conducted by psychologists on the behavioral and psychological aspects of cancer did not begin in earnest until the late 1970s. Yet considerable advances have been made in describing the difficulties cancer patients face and examining the processes of adjustment (see discussions in Andersen, 1989; *Cancer*, 1991, Vol. 67, No. 3 Supplement). Much of the

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Robert M. Kaplan served as action editor for this article.

psychological research in cancer rehabilitation has been aimed toward preventing or reducing the psychological and behavioral burdens and improving quality of life. Although there are differing definitions, the term *quality of life* is a multidimensional construct that includes functional ability (activity), psychological functioning (e.g., mental health), social adjustment, and disease- and treatment-related symptoms. Thus, psychologists who study oncology focus on behavioral outcomes, as has been advocated (e.g., Kaplan, 1990).

A Biobehavioral Model

Several recent review articles, both qualitative (Kiecolt-Glaser & Glaser, 1988b;O'Leary, 1990; Weiss, 1992) and quantitative (Herbert & Cohen, 1993a, 1993b), have concluded that psychological distress and stressors (i.e., negative life events, both acute and chronic) are reliably associated with changes, that is, downregulation, in immunity.[1] Considering these and other data, we offer a biobehavioral model, shown in Figure 1, of adjustment to the stresses of cancer and propose mechanisms by which psychological and behavioral responses may influence biological processes and, perhaps, health outcomes. For simplicity, many paths move in one causal direction. We discuss, in turn, each component and pathway in the model.

The Cancer Stressor and Psychological Pathways

A cancer diagnosis and cancer treatments are objective, negative events. Although negative events do not always produce stress and an altered quality of life, data from many studies document severe emotional distress accompanying these cancer-related events. Several years ago, we studied gynecologic cancer patients within days of their diagnosis and prior to treatment (Andersen, Anderson, & deProsse, 1989a). Using the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981), we found that the scores for women with cancer were significantly greater than scores from matched women who were awaiting treatment for benign gynecologic diagnoses, which in turn were higher than the stresses of everyday life reported by a matched group of healthy women. These data underscore the acute stress of a life-threatening diagnosis. However, it is also clear that lengthy cancer treatments and the disruptions in major life areas that subsequently occur can produce chronic stress. For example, in a study of 60 male survivors of Hodgkin's disease, long after treatment had ended, men reported lowered motivation for interpersonal intimacy, increased avoidant thinking about the illness (which is a characteristic of posttraumatic stress), illness-related concerns, and difficulty in returning to predisease employment status (Cella & Tross, 1986). Also, the majority of the patients (57%) reported low levels of physical stamina (Yellen, Cella, & Bonomi, 1993). Other permanent sequelae from cancer treatments, such as sexual problems or sterility (e.g., Kaplan, 1992), which have ramifications for intimate relationships and social support, are well documented (see Andersen, 1986, for a review). Unemployment, under-employment, job discrimination, and difficulty in obtaining health insurance can be problems for a substantial minority (e.g., 40% of bone marrow transplant survivors reported difficulty in obtaining insurance; Winegard, Curbow, Baker, & Piantadosi, 1991). Thus, many chronic stressors (e.g., continued emotional distress, disrupted life tasks, social and interpersonal turmoil, and fatigue and low energy) can occur with cancer.

We have considered the qualities of stressors that not only cause distress and a lowered quality of life, but that are also powerful enough to produce biological changes. Some of the effects may covary with the extent of the disease (which usually necessitates more radical treatment).[2] Considering psychological factors, Herbert and Cohen's (1993b) recent meta-analysis of the stress and immunity literature provides clarification. Their comparison of objective stressful

[1]Stress-associated changes in immune function occur as a result of the physiological changes that take place (i.e., alterations in levels of hormone and neuropeptides). These changes ultimately affect different aspects of immune function.

events, such as bereavement, divorce, or caregiver stress, with self-reports of stress, such as reports of hassles, life events, or perceived stress, revealed that greater immune alteration (e.g., lower natural killer [NK] cell activity) occurred with objective events. Furthermore, analyses of stressor duration showed that long-term naturalistic stressors (e.g., bereavement) may have a more substantial impact on NK cell function than do short-term stressors. Also, when events have interpersonal components, they too are related to greater immune alteration than are nonsocial events. The specific immune alterations that were sensitive to these stressor characteristics were NK cell activity, the helper:suppressor ratio, and the percentage of suppressor/cytotoxic T cells. Considering the objective, acutely stressful events of diagnosis and treatment and the chronic and interpersonally disruptive aspects of cancer recovery and survivorship described above, it would appear that cancer as a stressor includes the attributes that have documented linkages to immunity. Lowered NK cell activity may represent one of the more reliable markers of this process.

Behavioral Pathways

Health behaviors—Evidence suggests that there are health behavior sequelae for individuals experiencing psychological stress from cancer (the arrow from stress to health behaviors in Figure 1). Distressed individuals often have appetite disturbances that are manifested by eating less often or eating meals of lower nutritional value. For example, in a survey of 800 cancer patients being cared for at home, 38% reported regular problems with a loss of appetite, which they reported as unrelated to other problems they were having, such as nausea or vomiting (Wellisch, Wolcott, Pasnau, Fawzy, & Landsverk, 1989). Individuals who are depressed, anxious, or both are also more likely to self-medicate with alcohol and other drugs; alcohol abuse can potentiate distress (Grunberg & Baum, 1985). Distressed individuals often report sleep disturbances, such as early morning awakening, sleep onset insomnia, or middle-night insomnia (Lacks & Morin, 1992). In a study of long-term survivors of Hodgkin's disease, 27% of the sample reported continuing sleep problems (Cella & Tross, 1986). Cigarette smoking and caffeine use, which often increase during periods of stress, can intensify the physiologic effects of psychosocial stress, such as increasing catecholamine release (Dews, 1984;Lane & Williams, 1985). In sum, poor health behaviors may potentiate the effects of stress, and their co-occurrence for the cancer patient may add psychological and biological burdens.

Cancer stressors may influence the initiation or frequency of positive health behaviors. Exercise is one important example, as reliable associations have been found between mental health and physical activity, and exercise can be an important primary or adjunctive therapy for mood disorders, including anxiety- and depression-related problems (Dubbert, 1992; LaPorte, Montoye, & Caspersen, 1985). To the extent that cancer patients engage in sufficient, regular exercise to secure these benefits, the psychologic effects of stressors may be lowered. In fact, positive mood effects as well as increased functional capacity have been found for

[2]The extent of disease or staging refers to the assignment of cancers to an appropriate category or stage according to their apparent local, regional, and distant anatomic extent. Stage groups are provided for cancers of similar anatomic sites, and prognosis is closely related to stage. Staging is a convenient means of communication, allowing easy identification of cancers of similar extent and prognostic importance. Staging also provides a logical means of selecting treatment options. There are several systems for cancer staging. The simplest one divides cancers into three categories. *Localized* indicates that the cancer is confined to the organ of origin (e.g., the cervix, the ovary, the breast, the prostate). *Regional* connotes that a spread beyond the organ of origin has occurred (e.g., to lymph nodes from the breast, to the seminal vesicles from the prostate), but not to distant sites. Regional spread may have occurred by direct growth to adjacent organs or tissues (e.g., from the ovary to the Fallopian tubes), by metastasis to regional lymph nodes, or by spread to both regional tissues and lymph nodes. *Distant spread* means that there is metastatic disease to locations distant from the organ of origin (e.g., from the ovaries to the lungs, from the prostate to the bone, from the larynx to the brain). Another staging system uses Roman numerals, and that system generally uses Stage I and II for localized diagnoses, Stage III for regional, and Stage IV for distant (metastatic) disease. As indicated, survival is closely related to stage of disease at diagnosis. As a rule of thumb, survival rates drop by approximately 50% when moving from one successive stage to another. Obvious exceptions are the more deadly forms of cancer, such as lung or pancreatic, which have dismal survival rates even when the disease is localized. The most common type of survival estimates are those for five years from diagnosis—that is, the percentage of individuals diagnosed with the specific site or stage of disease who will be alive five years following diagnosis and treatment. For illustration, Table 1 provides survival rates for common tumors.

breast cancer patients receiving chemotherapy and participating in a program of aerobic interval training (MacVicar, Winningham, & Nickel, 1989). Even so, exercise initiation and maintenance is difficult to achieve, even among young and healthy persons (Sallis et al., 1986), and so it may be more difficult for cancer patients, who as a group are older, symptomatic from the disease or treatments, and distressed. Also, the high frequency of other problems, particularly fatigue (Pickard-Holley, 1991; Rhodes, Watson, & Hanson, 1988), may make it difficult to mobilize oneself to engage in positive health behaviors.

The contribution of stress to the alteration of health behaviors is made more complex by the direct effect that cancer treatments may have on some behaviors. For example, sensory changes may occur with radiation therapy (Smith, Blumsach, & Bilek, 1985) or chemotherapy (Bernstein, 1986), but they may occur at other times as well (Andrykowski & Otis, 1990). In turn, changes in eating patterns are well documented, with disruption and weight loss associated with learned taste aversions and changes in taste or smell acuity, as well as anorexia. Frequent clinical abnormalities that affect nutritional habits include elevated thresholds for sweet and salty tastes and lowered thresholds for bitter taste. The pathophysiology of weight loss, in particular, is not entirely understood but may be explained in part by the direct and interactive effects of energy balance and altered carbohydrate or protein metabolism (DeWys, 1982, 1985) from learning processes (Bernstein, 1986) as well as disease processes.

In the study of stress–immunity relationships, health behaviors as noted here are not always assessed, even though they may account for variance in immune function. We usually do not find that group differences in health behaviors between stressed and nonstressed samples are reliably related to immunological data in non-cancer samples, including medical students (e.g., Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984), divorced adults (e.g., Kiecolt-Glaser, Fisher, et al., 1987), and Alzheimer's disease caregivers (e.g., Kiecolt-Glaser, Glaser, Dyer, et al., 1987); this may be due in part to stringent health-screening criteria to control or rule out such factors at intake. In cancer studies, the omission of health–behavior variables has been unfortunate at times, as health–behavior mechanisms or compliance have been offered post hoc for some of the most notable findings (e.g., Spiegel, Bloom, Kraemer, & Gottheil, 1989).

Accumulating evidence exists for the direct effect of health behaviors on immunity (see arrow from health behaviors to immunity in Figure 1). The covariation of immunity and objective measures of sleep (Irwin, Smith, & Gillin, 1992), alcohol intake (MacGregor, 1986), smoking (Holt, 1987), and drug use (Friedman, Klein, & Specter, 1991) has been found. Moreover, problematic health behaviors can interact to further affect immunity. For example, substance abuse has direct effects on immunity (Jaffe, 1980), as well as indirect effects through alterations in nutrition (Chandra & Newberne, 1977). Poor nutrition is associated with a variety of immunological impairments, including cell-mediated immunity, phagocyte function, and mucosal immunity (Chandra & Newberne, 1977). In contrast, there is growing evidence that physical activity may also have positive immunological and endocrinological consequences, even among individuals with chronic diseases. For example, LaPerriere et al. (1990) showed a relationship between more positive immune responses and exercise and fitness in HIV-infected men. Thus, we posit that health behaviors are one plausible mechanism by which stress influences immune parameters.

Compliance—A second important behavioral pathway is (non)compliance. Data suggest that psychological or behavioral effects of cancer treatments can be so disruptive that patients become discouraged and fail to complete, or even refuse, treatment (see the arrow from stress to compliance in Figure 1). Noncompliance is a general health problem that crosses disease, treatment, and individual patient characteristics (e.g., Haynes, Taylor, & Sackett, 1979). It has, however, received relatively little research attention in cancer studies despite the potential of dramatic, negative consequences. Among the broader implications is the invalidation of clinical

trials (Haynes & Dantes, 1987), and, for the individual patient, treatment noncompliance can result in a lowered chance of survival. Data from Bonadonna and Valagussa (1981) clearly demonstrated this latter effect, with differential survival rates for women receiving more than 85%, 65%–84%, or less than 65% of the recommended dosages of cyclophosphamide, methotrexate, and 5–fluorouracil (CMF) therapy for breast cancer. This was not a study of non-compliance per se, as the reasons for dosage reduction included toxicity (32%), refusal of treatment (8%), age (i.e., more than 60 years old; 10%), and other reasons (33%; e.g., desire to simplify drug administration). However, it illustrates the impact on survival that therapy alterations can have. Also, some reasons for therapy alterations may be correlated with the psychological and behavioral aspects of noncompliance (e.g., treatment toxicity related to emotional distress), whereas others may not be (e.g., physician preference, ease of administration, patient age). Within the context of cancer therapy, compliance will have many representations, and it is likely that there are different correlates for different behaviors. Predictors of compliance with appointments for chemotherapy regimens have included variables within the quality of life domain, including difficulty in coping with symptoms, symptom interference with normal activities, or depression (Richardson, Marks, & Levine, 1988), as well as non-quality of life variables, such as length of treatment regimen (Berger, Braverman, Sohn, & Morrow, 1988). Similarly, predictors of chemotherapy drug levels have included treatment environment (lower compliance in community vs. university clinics; Lebovits et al., 1990), income level (Lebovits et al., 1990), and complexity of the regimen (Richardson et al., 1987). Review of the non-cancer literature affirms the generality of these findings and underscores quality of life factors, such as increased disability, as well as characteristics of the disease (i.e., frequency of symptoms) and regimen (i.e., duration and complexity of treatment), as correlates of noncompliance (DiMatteo & DiNicola, 1982). In contrast, global personality factors have not proved to be illuminating (Kaplan & Simon, 1990); instead, social factors might be important (Dunbar-Jacob, Dwyer, & Dunning, 1991).

The model also notes that poor compliance can affect local control (arrow from Compliance to Disease: Local in Figure 1) as well as distant control of the disease (arrow from compliance to disease: metastatic in Figure 1). The selection of the route(s) would depend on characteristics of an individual's noncompliance for the particular treatment regimen. Noncompliance leading to failure of local control includes the following examples. Irregular daily attendance to radiotherapy would allow more time for regeneration of cancer cells at the tumor site, reversing the balance that is in favor of normal tissue cell repair in a course of fractionated radiotherapy. Or, premature termination of the course (e.g., quitting therapy after 4 weeks of a 6-week course) would increase risk for local failure (i.e., disease-involved tissue at the primary site might not receive an adequate dosage to affect the biologic status of the tumor). Noncompliance leading to failure of metastatic control could include the following examples. Not ingesting systemic chemotherapy may lead to a more rapid spread of micrometastases, because therapeutic drug levels would not be achieved at the cellular level. Or, a patient may comply with initial therapy but fail to return for follow-up and thus lengthen the time of detection and treatment of recurrent disease; in many tumors, such as those caused by ovarian cancer, success at re-treatment is directly related to tumor volume.

Figure 1 also has a double-headed arrow between compliance and health behaviors, suggesting that the factors may interact; even synergy is possible. That is, those cancer patients who are compliant may expect better health outcomes and because of this may find it easier to comply with diet, exercise, sleep, and so forth, or to engage in other behaviors indicative of "good health." Conversely, those individuals who are noncompliant with therapy may have poor linkages to the health care system, and they might not receive information on, for example, diet, that others might receive during treatment or follow-up. The interaction of behavioral phenomena such as these and the effect of the personality factors that may govern them (e.g., conscientiousness; see relevant discussion in Friedman et al., 1993, or Andersen, in press) may

account in part for the positive main effect for compliance in randomized clinical trials of drug versus placebo for coronary heart disease. That is, better disease outcomes are found for placebo-compliant versus placebo-noncompliant patients, along with the expected finding of better outcomes for compliant versus noncompliant patients who receive active drugs (Coronary Drug Project Research Group, 1980;Epstein, 1984).

Biological Pathways

A variety of data suggest that stress sets into motion important biological effects, including those influencing the autonomic, endocrine, and immune systems. As illustrated in Figure 1, stress may be routed to the immune system by the central nervous system (CNS) by activation of the sympathetic nervous system (adrenergic nerves terminating in the lymphoid organs; Felten & Felten, 1991;Felten et al., 1987) or through neuroendocrine-immune pathways (i.e., the release of hormones). In the latter case, a variety of hormones released under stress have been implicated in immune modulation. Examples include the catecholamines epinephrine and norepinephrine, which are secreted by the adrenal medulla; cortisol, which is secreted by the adrenal cortex; and growth hormone prolactin and endogenous opioid peptides, produced by the pituitary, the adrenal medulla, the brain, or the immune system itself (see Baum, Grunberg, & Singer, 1982;Bonneau, Sheridan, Feng, & Glaser, in press;Cohen & Williamson, 1991;Morley, Benton, & Solomon, 1991;Rabin, Cohen, Ganguli, Lysle, & Cunnick, 1989;Sabharwal et al., 1992).

Regardless of the impact of stress, the immune system may be one of the more important biological determinants in the control of certain malignant diseases. There is considerable evidence for both the classical and natural immune responses in host resistance against progression and metastatic spread of tumors. In fact, the evidence for some components of the immune system, for example, NK cells, is more compelling in controlling metastases than for surveillance (Herberman, 1991). The presence of cancer can induce antitumor immune responses involving T cells, antibody-producing B cells, or both. Also, tumor-bearing individuals may have general alterations in their immune system, with depression of a variety of immunological activities, such as decreased cellular immune reactivity (as demonstrated in vivo by delayed cutaneous hypersensitivity and in vitro by lymphoproliferative responses to mitogen or alloantigens), decreased macrophage responsiveness (Cianciolo & Snyderman, 1983), and decreased NK cell activity. These impairments have been most consistent in patients with advanced, metastatic disease, but some studies have shown abnormalities among individuals with localized disease (Stein, Adler, & BenEfran, 1976). In addition to the alterations in cellular immunity noted above, cancer may affect the relative proportions and absolute numbers of T and B cells, as many cancer patients, including some with localized disease, have decreased percentages of T-cell subpopulations (e.g., Kikuchi, Kita, & Oomori, 1988). For our model, there are at least two important questions regarding stress–immune relationships: What is the evidence for either stress-mediated immune responses, and what is the evidence for stress-mediated health effects?

Evidence for a stress–quality of life mediated immune response—There are three lines of supporting data. First, time-limited (acute) stressors can produce immunologic changes in relatively healthy individuals. Data from our psychoneuroimmunology (PNI) laboratory studies with healthy medical students taking academic examinations have provided strong and reliable demonstrations of this effect. They have shown, for example, that during the stressful exam period, significant declines in NK cell activity and decreases in T-cell killing of Epstein-Barr virus (EBV)-infected target cells have occurred, along with dramatic decreases in gamma interferon production by lymphocytes stimulated with concanavalin A (Con A; e.g., Glaser et al., 1987; Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986).

Although the emotional distress of medical students taking exams and the distress of cancer patients have not been directly compared, convergent data support the acute emotional crisis with a life-threatening diagnosis and the correlated immune responses. For example, Ironson et al. (1990) prospectively assessed men taking the HIV-1 antibody test and found differential immune responses among men who tested seropositive and those who tested seronegative. As would be expected, men who tested seropositive reported significant acute anxiety responses and traumatic stress, with significant negative correlations between self-reported anxiety and NK activity (−.69).

Returning to cancer, we showed that for women with gynecologic cancer who had been assessed with the POMS, emotional distress within days of diagnosis and prior to their treatment was significantly greater than that for two relevant comparison groups (Andersen, Anderson, & deProsse, 1989a). A follow-up study (Andersen & Turnquist, 1985) on the covariation of affective distress and immunity was conducted with newly diagnosed but as yet untreated cervical and endometrial patients. On the first visit to the tertiary care hospital for their diagnostic workup, women's emotional distress was assessed with the POMS, and a morning blood sample was drawn. A subgroup of the women had a repeat blood sample drawn approximately 10 days later, on the day before surgery. First, differences between disease sites were examined; no emotional distress or immune variable or white blood cell (WBC) count differed significantly. However, because differential immune effects for sites are unknown, within-site analyses were conducted. Using a hierarchical multiple regression model, total mood disturbance on the POMS significantly predicted WBC counts at the initial and presurgery assessments beyond that predicted by the relevant disease risk, stage, and immune-moderating factors. Additional analyses with the POMS Depression subscale revealed similar significant relationships at both the initial and the presurgery assessments. These effects were replicated for the endometrial sample; the POMS was significantly related to WBC counts at the initial assessment, and depression and confusion were related to WBC counts at presurgery. These data were encouraging as they were the first tests of covariation of emotional distress and one general measure of immune status in cancer patients prior to their treatment. Also, the subscales that the prospective longitudinal study had indicated as relevant for women with cancer (Depression and Confusion; Andersen, Anderson, & deProsse, 1989b) were also relevant for the prediction of WBC counts.

More recent data replicated and extended these findings (Roberts, Andersen, & Lubaroff 1994). Subjects were women with cervical (Stage I, $n = 27$; Stage II, $n = 10$) or endometrial (Stage I, $n = 17$; Stage II, $n = 4$) cancer assessed on two occasions (separated by approximately one week) following their diagnosis and prior to treatment. Distress measures included self-reported distress (POMS) and interviewer-rated distress and disturbance of affect (a modified version of a Schedule for Affective Disorders and Shizophrenia—SADS; Endicott & Spitzer, 1978—interview) to address inconsistencies in previous research (e.g., Levy, Herberman, Maluish, Schlein, & Lippman, 1985). Twenty age-matched healthy women were included to validate emotional distress indicators. Descriptive analyses indicated that, as expected, cancer subjects exhibited greater psychological distress across all measures. A multivariate analysis of variance (MANOVA) for the quantitative immune measures revealed significant differences between WBC and NK, with follow-ups indicating increased WBC counts and decreased numbers of large unclassified (NK) cells between the cancer group and healthy group. Regression analyses focused on the prediction of large unclassified (NK) cell counts. As before, relevant variables correlating with outcome (i.e., cell counts at Time 1, age, stage, and a functional performance rating) were entered as prior steps. Thirty-two percent of the variance was predicted, with the final step of the POMS and interviewer-rated distress ratings accounting for an additional, significant 17% of the variance in predicting large unclassified cell counts at the second assessment. In sum, data from healthy, HIV-infected, and cancer subjects indicate

that the occurrence and magnitude of stress accompanying time-limited stressors or acutely stressful periods is correlated with at least certain aspects of immune downregulation.

Second, chronic stressors are associated with continuing downregulation of immunoresponsiveness rather than adaptation. This effect is evident in longitudinal studies for a range of lengthy or permanent stressors, including environmental stressors, such as living next to a damaged nuclear reactor (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989), or PNI laboratory studies of close relationship failures (e.g., divorce, separation, or marital distress; Kiecolt-Glaser, Fisher, et al., 1987) and caregiving for a family member with progressive dementia (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). In the latter example, quality of life factors (the caregivers' social support) moderated immune functioning. Again, direct comparisons between chronic stressors of this sort and cancer have not been made, but we have noted the many commonalities between these chronic stressors and the cancer experience.

One implication of the chronic stressor data reported thus far is that the immune changes associated with the stressor do not habituate. For example, recent PNI data from the Alzheimer caregiver study showed lower NK cell cytotoxicity in caregivers than in controls when NK cells were stimulated by interferon gamma; similar results were obtained with the generation of lymphokine-activated killer (LAK) cells by interleukin-2. Moreover, even after the chronic stresses of caregiving had ended, bereaved caregivers did not differ from continuing caregivers; both groups had significantly lower NK-augmented cytotoxicity than did the controls (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, in press), suggesting nonhabituating stress effects for bereaved persons. The latter data parallel Baum's (1990) data on the longer-term downregulation in immune function among residents who continue to live next to the Three Mile Island nuclear reactor. The physiological effect of long-term secretion of stress-relevant hormones (e.g., catecholamine) has been noted, with the result that neuroendocrine receptor number and availability is altered (Baum, 1990; Sapolsky, Krey, & McEwen, 1986). Assuming a continuously interactive system, such changes could in turn result in a new, lower baseline.

Convergent evidence from several laboratories suggests that a psychological factor—social support—may interact with chronic stressors to produce differences in sympathetic nervous system (SNS) reactivity, neuropeptide release, and immune function. Our data indicate that family caregivers of relatives with Alzheimer's disease who are high in social support display different patterns of age-related heart rate reactivity and blood pressure than do caregivers who are low in social support (Uchino, Kiecolt-Glaser, & Cacioppo, 1992). Our earlier data from the same sample had shown that caregivers had poorer immune function than did controls and that low social support was associated with greater declines in immune function over the course of a year (Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992). Similarly, Irwin, Brown, et al. (1992) found higher levels of neuropeptide Y (NPY) in Alzheimer's disease caregivers than in controls; levels of NPY, a sympathetic neurotransmitter released during emotional stress, were inversely correlated with NK cell activity. Related data come from a study of social support among wives of cancer patients. Baron, Cutrona, Hicklin, Russel, and Lubaroff (1990) have shown greater immunocompetence on two of three measures (NK cytotoxicity and phenohemagglutin, PHA, but not Con-A) among those wives reporting higher levels of social support.

Chronic stress has also been implicated as a factor in enhanced cardiovascular reactivity as well as in higher levels of urinary catecholamine in two studies from Baum's laboratory (Fleming, Baum, Davidson, Rectanus, & McArdle, 1987; McKinnon et al., 1989). Because individuals with high cardiovascular reactivity appear to show magnified endocrine and cellular immune responses to experimental psychological stressors (Kiecolt-Glaser et al.,

1991; Sgoutas-Emch et al., in press), enhanced SNS reactivity could have important physiological consequences.

In addition to these biological mechanisms, which could serve to maintain downregulation of certain aspects of immune function, behavioral adaptations made in the lengthy coping process could produce related effects on immunity. Some coping behaviors may be adaptive but others may not be, or it may be difficult (or impossible, in some cases) to resume prestressor adjustment levels. For example, the behavioral data from the longitudinal study of Alzheimer's disease caregivers indicates that former caregivers who now are bereaved show similarly high rates of syndromal depression, depressive symptoms, and lower social support as do the continuing caregivers, with both of these groups having significantly poorer immune function than age-matched noncaregivers (Esterling et al., in press). Although early surveys suggested that well-being increased once caregiving ended (George & Gwyther, 1984), our longitudinal data indicate no reconstitution of social networks, but rather the continuation of intrusive and avoidant thoughts about the experience for as long as two years after the disabled relative's death (Bodnar & Kiecolt-Glaser, in press). Similarly, Baum and his colleagues (Fleming et al., 1987) found that when chronic stress was associated with avoidant or intrusive thinking about the stressor, enhanced cardiovascular reactivity was one possible consequence. These findings are consistent with other data on environmental stressors that suggest that long-term stressors may erode social support (Lepore, Evans, & Schneider, 1991) and have continuing, negative, cognitive effects. Taken together, however, they provide suggestive evidence for several pathways through which behavioral mechanisms could promote continued immune downregulation in concert with long-term stressors.

Third, studies with cancer patients provide data linking quality of life components and immunity. In an early study by Levy et al. (1985), 75 women with Stage I or II breast cancer were assessed following surgery (lumpectomy or mastectomy with node dissection) and before initiation of other therapy. Women who were rated as better adjusted to their illness but who reported higher fatigue (as assessed with the POMS) had lower NK cell levels. Another study (Levy et al., 1990) reported on different psychosocial variables at three months after treatment (lumpectomy or mastectomy with or without adjuvant therapy) for 66 women with Stage I or II disease. In addition to estrogen receptor status (an important prognostic indicator) predicting NK cell lysis, social support added significantly to the model in predicting higher NK cell activity. These data are somewhat inconsistent but are generally in line with data from healthy individuals with positive indicators of quality of life (e.g., social adjustment) predicting higher NK cell levels and negative–distress indicators (e.g., emotional distress) predicting lower NK cell levels.

Finally, relevant animal studies have come from the laboratory of Liebeskind and colleagues (Ben-Eliyahu, Yirmirya, Liebeskind, Taylor, & Gale, 1991) that suggest a link between pain-induced immune suppression of NK cell activity and the development of syngenetic mammary tumors. In this model, tumor development and metastatic spread has been shown to be significantly controlled by NK cells. Using Fisher rats that were exposed to an acute stressor (pain from surgery), a substantial decrease in NK cell lysis in vitro was found using the tumor cells as target cells. When in vivo studies were performed using animals undergoing the surgery stressor, there was a decrease in NK cell cytotoxicity concomitant with an increase in tumor metastases. Although the applicability of animal tumor data to cancer processes in humans is complex and best achieved with narrow, hypothesis-driven comparisons (Moulder, Dutreix, Rockwell, & Sieman, 1988), these animal data support stress-induced modulation of certain aspects of the immune system (i.e., NK cells) known to be important for surveillance and tumor control.

Evidence for stress or decrements in quality of life having health consequences—Two lines of data suggest negative health consequences. Some investigators have tested the direct role of stress, whereas others have tested an indirect route through immune indicators. First, there is solid evidence for the link between acute stress and illness, specifically, infectious illness in young, healthy individuals. Cohen, Tyrrell, and Smith (1991) inoculated 357 volunteers with either a cold virus 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 using five different strains of "cold viruses," providing a controlled demonstration of increased infection associated with increased stress. Consistent with Cohen's data, we found that stress influenced medical students' responses to a hepatitis B vaccination. Students received each of three injections of the vaccine on the last day of a three-day examination period to study the effects 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 seroconverted (produced an antibody response to the vaccine) after the first injection; early seroconverters were significantly less stressed and less anxious than those students who did not seroconvert until 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 the virus and a virus-specific T-cell response to a purified viral polypeptide. Thus, these data suggest that the immune response to a vaccine (and, by extension, to other primary antigens) can be modulated by a mild stressor—even in young, healthy adults who have a long history of exposure to (and mastery of) this very stressor. Moreover, these data provide a window on the body's response to other pathogens, such as viruses or bacteria. The more stressed and more anxious students seroconverted later; these same individuals might also be slower to develop an antibody response to other pathogens and, in turn, be at risk for more severe illness.

Data are accumulating for the health effects from chronic stressors. Data from our PNI laboratories (Kiecolt-Glaser et al., 1991) have shown that "at risk" Alzheimer caregivers (i.e., caregivers with consistent immune downregulation across functional assays) had more and longer-lasting upper respiratory tract infections than did the remainder of the sample. Baum (1990), using physicians' data, found that numbers of both physical complaints and prescriptions written for Three Mile Island-area residents were greater than those for control subjects for two years after the accident. Moreover, although physician-measured blood pressure had been comparable for Three Mile Island residents and controls in the year preceding the nuclear reactor accident, Three Mile Island-area residents showed greater elevations on both systolic and diastolic blood pressure than did controls in the year following the accident.

The few data from diagnosed cancer groups are most relevant. All of the health outcomes that have been studied have been disease endpoints. However, infections and infectious illnesses, for example, would seem relevant, as infectious pathogens are a major cause of morbidity and mortality for cancer patients (e.g., Innagaki, Rodriguez, & Bodey, 1974; Ketchel & Rodriguez, 1987). Although it is not an endpoint, the extent of disease at initial diagnosis (i.e., number of positive nodes) is important prognostically. Levy et al. (1985) found self-reports of fatigue (POMS) obtained shortly following initial treatment to be a predictor of nodal status in women with breast cancer, but there was no effect for fatigue if NK cell levels were first entered into the regression equation. We also examined disease progression to the lymph nodes in women with gynecologic cancer (Roberts et al., 1994). Unlike Levy et al.'s study, which confounded collection of distress and immunity data with knowledge of nodal status, here nodal status was learned afterward, approximately 16 days from the initial assessment (Time 1) and 5 days from the presurgery (Time 2) immune assessment. After the clinical stage and the two assessments of NK cell lysis, interviewer-rated disturbance of affect (i.e., blunted, inappropriate, and depressed affect) contributed significantly (14% of the variance) to the prediction of the number of positive nodes.

Psychological studies predicting cancer endpoints, however, have the most relevance for the model.[3] Levy, Herberman, Lippman, D'Angelo, and Lee (1991) examined variables predicting disease-free intervals (DFIs) and recurrence in 90 women with initial Stage I or II breast cancer with data gathered at postsurgery and at 3-and 15-month follow-ups. DPI was predicted by number of positive nodes (−.27) and distress (POMS; −.41) at 15 months, with neither NK cell lysis at postsurgery nor 15 months later as significant predictors. In contrast, POMS scores did not predict recurrence; instead, recurrence was predicted by NK cell activity at postsurgery (−.35) and 15 months later (.75). Finally, Levy, Lee, Bagley, and Lippman (1988) examined time to death following recurrence for 36 women with breast cancer. Along with the medically relevant variables of DFIs, physician-rated prognosis, and number of metastatic sites, positive affect (Joy) reported at recurrence predicted a longer survival time.

Summary

Data from healthy samples suggest that stress variables are predictive of immune downregulation, and accumulating data with cancer groups support the same general conclusion. Because the phenomena appear to be reliable, investigators are beginning to examine the clinical relevance of the effect. That is, are these immune changes related to health consequences? Here the data are sparse, but the most controlled analysis, the study by Cohen et al. (1991), shows a direct, replicable relationship between stress and infections and colds. Many researchers question whether the latter findings are relevant to persons with cancer or to those with other chronic illnesses, such as HIV infection or AIDS. The most frequent argument waged against psychological and behavioral effects (even if large) significantly affecting biologic processes is because of the presumed downregulating effects of the disease or the treatments. That is, both our data and those of Levy and colleagues come from correlational designs that tested the contribution of psychological factors, and the directional hypotheses for all variables—psychological–behavioral and disease–treatment effects—are in the same direction, downregulation.

In this context we offer one observation and one suggestion for continued study. First, the directional effects of cancer on the immune system remain to be documented; however, there are sufficient data to state that cancer effects are not unidirectional (i.e., downward), within or across sites. For example, T-cell levels may be slightly decreased, whereas T-cell function appears to be intact in early stage ovarian cancer (Mandell, Fisher, Bostick, & Young, 1979). In contrast, cervical cancer patients often have an increase in B cells and gamma interferon levels, with a decrease in T-cell function (Sharma, Gupta, & Kadian, 1979). Variability on other immune measures, such as delayed hypersensitivity to antigens and contact allergens, can occur across cervical, endometrial, and ovarian cancers (Khoo, MacKay, & Daunter, 1979; Nalick, DiSaia, Rea, & Morrow, 1974). The model we and other psychologists test, however, is in line with the immune theory that posits an influential role of NK cells in host resistance against metastasis (Gorelik & Herberman, 1986). The latter theory rests on the association between depressed immune activity and increased metastases in animal models.

We have proposed a biobehavioral model of variables and pathways believed to lead to immune and health effects. Regarding the health effects, we have discussed disease progression and related variables (e.g., DFI) as endpoints; however, the model may be relevant to other health

[3]In clinical cancer research, a major research design decision is the selection of the important endpoint, or criterion, to be predicted. Survival time (time alive since diagnosis and treatment) is one of the most common, but often is not the most helpful because of the variable course of most cancers. Endpoints fall into four broad categories. Response to therapy includes, for example, judgments of complete response, partial response, stable disease, and failure or progression of disease. Time intervals associated with control of disease include disease-free interval following initial therapy, survival, disease-free survival, interval of local control, or time before development of metastatic disease. Toxicity-related endpoints also are considered, such as degress of therapy modification because of toxicity, highest grade of toxicity encountered, occurrence and grade of late effects, and time to appearance of late effects. Finally, there is increasing interest in establishing quality of life endpoints in cancer.

outcomes, such as a higher incidence of infections and infectious (viral) illnesses (infections are a major obstacle in health care management of cancer patients and also are a major cause of death; Bodey, 1986). Further correlational studies of diagnosed cancer patients would need to be performed to document the reliability of the stress–immunity–cancer link. However, a stronger test would be, of course, to experimentally manipulate a variable in the model. Despite the numerous difficulties entailed, a randomized intervention trial offers a powerful test. A psychological–behavioral intervention is powerful because the prediction for the intervention would be for immune enhancement, more positive health outcomes, or both, in contrast to the prediction for a no-treatment control of downward regulation, poorer health outcomes, or both.

We have reviewed the effects of psychological interventions on moderating immunity in noncancer populations (Kiecolt-Glaser & Glaser, 1992). There we noted that researchers have used diverse strategies to modulate immune function, including relaxation, hypnosis, exercise, self-disclosure, and cognitive–behavioral interventions, and these interventions have generally produced positive changes. For example, our PNI laboratory tested the immune effects of a relaxation training and social contact intervention (Kiecolt-Glaser et al., 1985) with a cancer-relevant sample, elderly adults (mean age of 74 years) living in independent living facilities. Subjects were randomized to (a) relaxation training, (b) social contact, or (c) no contact. Subjects in the two intervention conditions were seen individually three times a week for a month (12 sessions). Blood samples and self-report data were obtained at pretreatment, posttreatment, and one-month follow-up. Analysis of the the psychological data indicated that the relaxation intervention had quality of life effects, as indicated by significant reductions on the Hopkins Symptom Checklist (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974), a measure of affective distress. Also, all subjects (including controls) reported a significant increase in self-rated quality of sleep, a positive health behavior. Analyses of the immune data indicated that the relaxation intervention produced significant increases (approximately 30%) in NK cell activity (see Figure 1 in Kiecolt-Glaser et al., 1985), with the highest percentage lysis of target cells occurring immediately after treatment. It is because of promising data such as these (see Kiecolt-Glaser & Glaser, 1992, for a review) that we conclude with a brief discussion of the role psychological interventions may play in answering stress and immunity questions in cancer.

Testing the Model

Research Design: A Role for Experimental Trials of Psychological and Behavioral Interventions

We have previously reviewed the evidence for psychological and behavioral interventions with cancer patients (see Andersen, 1992, for a discussion). Several controlled trials have demonstrated that such efforts can reduce distress, hasten resumption of routine activities, and improve social outcomes for groups at high risk for quality of life morbidity, such as patients with disseminated or recurrent disease, as well as patients at lower risk, such as those with localized disease and time-limited cancer therapy. We have suggested here that appropriately designed psychosocial interventions can reduce stress and enhance quality of life as well as improve behavioral responses, such as health behaviors and compliance. This research progress in behavioral oncology—the prospect of randomly assigning individuals to conditions that will result in differential psychological and behavioral outcomes— provides one of the necessary conditions for an experimental test of the model.

Therapy components for psychological interventions have included an emotionally supportive context to address fears and anxieties about the disease (e.g., Cain, Kohorn, Quinlan, Latimer, & Schwartz, 1986; Capone, Good, Westie, & Jacobson, 1980; Forester, Kornfeld, & Fleiss, 1985; Maguire, Brooke, Tait, Thomas, & Sellwood, 1983), information about the disease and treatment (e.g., Cain et al., 1986; Fawzy et al., 1990; Houts, Whitney, Mortel, & Bartholomew,

1986; Jacobs, Ross, Walker, & Stockdale, 1983; Maguire et al., 1983), behavioral coping strategies (e.g., role playing difficult discussions with family or the medical staff; Fawzy et al., 1990; Houts et al., 1986), cognitive coping strategies (Cain et al., 1986; Davis, 1986; Houts et al., 1986; Telch & Telch, 1986), relaxation training to lower "arousal" or enhance one's sense of control (Davis, 1986; Fawzy et al., 1990), and focused interventions for disease-specific problems (e.g., sexual functioning for gynecologic or breast cancer; Capone et al., 1980).

It is more difficult to enumerate the intervention components that can affect health behaviors. Despite their importance, health behaviors have not been included as outcomes in cancer studies, even though many psychosocial interventions include educational components designed for them. Of the very few studies focusing on compliance per se, the data suggest similar interventions, including information about the disease and treatment (Richardson et al., 1987; Robinson, 1990), enlistment of help of significant others (i.e., social support; Richardson et al., 1987), and practitioner counseling (i.e., prompts by a physician to be compliant; Robinson, 1990). For reference, the extensive literature on compliance with antihypertensive regimens (e.g., Dunbar-Jacob et al., 1991) suggests different techniques for different compliance targets. Specifically, mailed reminders and home visits by nursing personnel have been used to improve appointment keeping, whereas education, behavioral strategies (e.g., self-monitoring, contingency contracting), and enhanced social support have been used to improve medication compliance.

In considering an experimental trial to affect immunity or disease endpoints, a simple experimental design—treatment versus no treatment—would be the strategic next step. At present, there are insufficient data to choose among intervention components that would be expected to affect the immune system, but these and related findings would suggest an emphasis on relaxation, coping, social support, and disease-specific components (Andersen, 1992; Kiecolt-Glaser & Glaser, 1992). Such a design would not provide the basis for ruling out secondary hypotheses of therapist characteristics separate from treatment techniques, patient characteristics separate from psychological and behavioral difficulties, or specific therapeutic techniques as separate from nonspecific or placebo effects. What it can do, however, is establish cause–effect conclusions for the presence of intervention-producing enhanced psychological and behavioral outcomes, immune responses, and health effects. Once an effect is reliably demonstrated, it would then be relevant to study component questions. In the interim, investigators should document the content, the reliability of intervention delivery, and the involvement of the patients, for hypothesis generation in follow-up studies. Previous studies have omitted documentation and process measures (but see Gordon et al., 1980, for an example of number of individual therapy sessions; or Telch & Telch, 1986, for monitoring of homework assignments).

There already is suggestive evidence in support of the model, with data that indicate positive immune and health consequences for psychological interventions, and taken together they provide a basis for further scientific inquiry. One study included immune measures and disease endpoints, and two others reported disease endpoints. All of the studies used extensive psychological assessments, but none examined behavioral variables (i.e., health behaviors and compliance). For the first study, Fawzy et al. (1990) studied newly treated Stage I or II melanoma patients randomly assigned to either no intervention or a structured short-term (10 sessions) group support intervention. At posttreatment and the six-month follow-up, significant psychological and coping outcomes for the intervention subjects were evident, as well as increases in the percentage of large granular lymphocytes, the NK cell phenotype, an increase in NK cell numbers (as determined by markers), and other positive findings, such as interferon alpha-augmented NK activity. These data are relevant to the findings of Kiecolt-Glaser et al. (1985), who found intervention differences in NK activity. Importantly, the magnitude of the NK changes Fawzy et al. found was frequently greater than 25% for the intervention subjects.

Finally, the correlation data of immune and affective change provides additional support for the model in that interferon-augmented NK cytotoxic activity increased with concomitant reductions in anxiety (−.37) and depression (−.33). We believe the NK cell data are particularly important, because it has been shown that there is a reduction in NK cell activity with tumor progression (Akimoto et al., 1986; Takasugi, Ramseyer, & Takasugi, 1977). It is also known that the ability of NK cells to respond to interleukin-2 (IL-2) or gamma interferon is different in cancer patients who are managed with different types of therapy.

Six-year follow-up data on disease endpoints are also available (Fawzy et al., 1993). Analyses of DFIs to death have indicated significant group differences, with 29% of controls and 9% of experimental subjects dying in the six-year interval. Analyses of DFIs to recurrence were in the same direction but only approached significance ($p = .09$). Follow-up analyses suggested that the former effects were primarily due to the men in the control group dying and, in particular, men with the highest Breslow depth rating (a disease-related prognostic indicator; higher values indicate poorer prognosis). Considering the latter factor, 9 of 10 experimental subjects in the highest Breslow category were alive, versus only 1 of 9 control patients.

In the same follow-up, other analyses examined baseline and six-month psychological and immune parameters by survivor group and gender. The majority of the effects reside within the male group, so it is useful to consider the surviving versus the deceased males. These comparisons indicate that from baseline to the six-month assessment, the surviving males reported significant decreases in affective distress, increases in active behavioral coping, and increases in CD 16 NK cells and interferon alpha-augmented NK cell activity (i.e., immune up-regulation). In contrast, males who died showed no significant changes on any of these variables, that is, no quality of life improvement or immune enhancement. It also should be noted that the deceased males began the study reporting significantly lower overall levels of distress (i.e., 34 vs. 64 on the baseline Total Mood Disturbance of the POMS for the deceased vs. surviving males, respectively), but their immune responses were within the same range as those of the survivors.

Fawzy et al.'s (1990, 1993) investigation was the first intervention study to combine psychological, immune, and disease endpoint data. The initial outcome data indicated that early, brief psychological efforts produced immediate (posttreatment) effects as well as long term (six-month) changes. We have suggested that the maintenance of gains may be a crucial foothold for immune effects to emerge (Andersen, 1992); data from a relaxation intervention study suggest this as well. Gruber et al. (1993) studied 13 Stage I, node-negative breast cancer patients who received electromyograph (EMG) biofeedback-assisted relaxation training. Weekly immune assessments during the nine-week intervention indicated significant differences between the treatment and control groups in the expected direction: WBC values were stable for the intervention group but declined for the control, and Con-A and mixed lymphocyte response values were higher for the intervention group. NK cell values significantly increased from pre- to posttreatment. Considering immune data taken each of the nine study weeks, there was suggestive evidence that the immune effects became evident only after several weeks into the intervention.

Other data relevant to the model come from samples very different from these good prognosis patients. Specifically, women with recurrent breast cancer and lung cancer patients have been studied. Spiegel, Bloom, and colleagues (Spiegel, Bloom & Yalom, 1981; Spiegel & Bloom, 1983) randomly assigned women with metastatic breast disease to a no-treatment condition or to a group treatment condition that met weekly for at least one year. The intervention subjects were also randomly assigned to a no additional treatment condition or to a self-hypnosis condition for pain problems. The intervention group subjects reported significantly lower emotional distress (POMS) and fewer maladaptive coping responses than did the control

subjects, with the magnitude of the difference increasing during the intervention year. Data also suggested that the hypnosis component provided an additive analgesic effect to other group treatment components. A 10-year follow-up was conducted, at which time only three women, all of whom were intervention participants, remained alive (Spiegel et al., 1989). A striking survival difference was found between the control subjects (18.9 months) and the intervention subjects (36.6 months) from study entry until death. Survival time differences between the groups began to emerge approximately 8 months after termination of the year-long intervention.

As might be expected, the publication of Spiegel et al.'s (1989) survival follow-up study unleashed a torrent of interest in the role of psychological factors in cancer in both academic and popular circles (e.g., Moyers, 1993; ten Have-de Labije & Balner, 1991; Temoshok & Dreher, 1992). One critic of the findings, however, was LeShan (1991, 1992), who suggested that the survival effects might have been due to adverse effects on the control group (i.e., perceived rejection implied by being randomly selected out of the treatment group) rather than to positive effects on the intervention group. In fact, Fox's (1992) comparison of the study's survival data with national survival rate data has supported the implication of LeShan's concern: "The survival of the intervention group was somewhat worse than the survival of the national sample, while the survival of the control group was considerably worse (p. 83)." Despite this, Fox argued that it is unlikely that the control group died at a faster rate for "perceived rejection" reasons. He posited that this explanation is unlikely for several reasons, including the lack of national enthusiasm for group support interventions at the time of the study (late 1970s), no suggestion at all to the study participants that the study had any relevance to survival, and, more likely, that the differences reflect chance deviation of the entire study sample (consisting of only 84 women) from the population of women represented in national trends.

Finally, contradictory data come from Linn, Linn, and Harris (1982), who offered a death and dying intervention program to male cancer patients, 46% of whom had lung cancer. Despite favorable quality of life outcomes for the intervention subjects (e.g., lower distress [POMS], higher life satisfaction, lower alienation), there were no functional status or body system impairment differences between the control group and the intervention group. Survival analyses also revealed no significant differences. Aside from the many methodology differences between this and the Spiegel et al. (1989) study, two disease factors may account for the discrepancy in survival outcomes. First, there is a shorter survival window for metastatic lung cancer in contrast to metastatic breast cancer. (Five-year survival rates are 13% and 73%, respectively, for initial Stage III disease and 1% and 19%, respectively, for initial Stage IV disease; Boring et al., 1993.) Second, hormonal and immune factors may be more important in breast cancer than in lung cancer (see subsequent discussion below).

Methodology: Maximizing the Signal to Noise Ratio

It is an understatement to characterize this as "a most difficult area of research" (Fox, 1978, p. 117), and one that, like AIDS and HIV, is methodologically complex for behavioral immunology researchers (Kiecolt-Glaser & Glaser, 1988a). We cannot adequately address all of the methodology challenges that tests of the biobehavioral model pose; however, we reference here some of the more difficult ones at the interface of behavioral oncology and immunology and we refer the reader to other methodology discussions of variables predicting risk for psychosocial morbidity, and individual-differences variables that may covary with psychosocial outcomes or intervention effectiveness (Andersen, 1994, in press).

First, the term *cancer* refers to a heterogeneous group of diseases of multiple etiologies that vary in their tissue of origin, cell type, biologic behavior, anatomic site, and degree of differentiation (stage and degree of malignancy). Although we have used the generic term

cancer in this article, it is likely that quality of life and stress and health behavior factors would interact with immune function only in selected cases. Many hypothesized cancer-causing mechanisms are associated with immunological down-regulation. However, the likelihood of psychological or behavioral factors interacting with the immune system to influence disease progression would be expected to differ across sites. Cancers that are etiologically linked to hormonal stimuli (e.g., breast, ovarian, endometrial, and prostate) or to the immune system (e.g., leukemias, lymphomas) may be most susceptible to influence; Epstein-Barr virus (EBV)-associated tumors (i.e., EBV-associated B cell lymphomas; Levine, Ablashi, Nonoyama, Pearson, & Glaser, 1987), viral (e.g., cervical; Goodkin, Antoni, Sevin, & Fox, 1993a, 1993b), and genetically linked forms (e.g., some types of breast and colon cancer) may be somewhere in the middle, and those cancers believed to be due to physical or chemical carcinogens (e.g., lung cancer linked to tobacco usage) may be the least susceptible to influence. Also, it is known that the risk of cancer increases with age, and as the immune system ages it becomes less efficient. It has been suggested that psychological and stress factors may be most relevant for middle-aged persons (ages 35–65) rather than for very young or very old persons, because of the disproportionate influence of hereditary factors on young cancer patients and the influence of aging factors on older persons (Fox, 1978).

Thus, the proposed model may evidence the best fit for some sites (e.g., breast, ovary, prostate), and even for some forms within sites, as opposed to others. Application of the model to other chronic illnesses would require further refinement. Testing of the model might be additionally optimized when samples are as homogeneous as possible on other major dimensions, such as prognostic factors; such variables might be chosen for stratification or at least for documentation (e.g., the case with Breslow depth in the Fawzy et al., 1990, 1993, study). Selection of variables would be based on their unique importance to the disease site being studied. This is the same tactic taken in moderate-sized clinical trials of medical therapies in which the effect of the prognostic variables is anticipated to be greater than the effect of the new cancer treatment. For most sites it is more feasible to stratify on disease or prognostic variables than to attempt to control for cancer treatment. There are diverse treatment regimens now available, and choices among them are made on several bases, including, but not limited to, current data on the treatment regimens' relationship with prognostic variables; patient choice, if possible; physician preference, expertise, or specialty; and data from new trials (e.g., new uses of Taxol are occurring on a monthly basis). Because this is the scenario for most of the prevalent disease sites (e.g., breast, prostate, colon), careful selection of major prognostic indicators can result in de facto control of treatment, even when the available cancer therapies change during the course of the study. For example, the variables of nodal status, hormone receptor status, and menopausal status might be considered for a study of women with breast cancer (see Clark & McGuire, 1992, for a discussion). These variables would, in various combinations, determine most of the treatment pathways, influencing, for example, the occurrence and extent of surgery, the type of chemotherapy for premenopausal (adjuvant chemotherapy) versus postmenopausal women (adjuvant Tamoxifen), or the likelihood of extreme treatments, such as bone marrow transplant.

Second, the model posits immune effects from psychological and behavioral factors beyond any immune downregulation that may accrue either from malignant disease processes or from cancer treatment effects. Some researchers believe intervention trials of this sort are misguided at best, because the immunosuppressive effects of the disease or treatments would override any positive effects from a psychological intervention. In fact, attempting to address this concern with evidence, such as determining the magnitude of immunosuppressive effects from disease or cancer treatments, is surprisingly difficult because of the dearth of basic immunology data. Also, data that is available is not always confirmatory. For example, Ludwig et al. (1985) found unaltered immune function in patients with nondisseminated breast cancer (Stages I through III) at diagnosis, with the significant reductions (e.g., depressed PHA

responsiveness) found only among women with metastatic (Stage IV) disease. Regarding cancer treatments—surgery, radiotherapy, chemotherapy, chemoradiation (chemotherapy that is radiosensitizing and given with radiation), and combination therapy—all have immunosuppressive effects, but much of the detail about the nature of the effects is unknown. It has been found that lymphocyte transformation is depressed during radiotherapy but may rebound within two months after therapy; there is also specificity due to site of treatment, as greater depression is found for pelvic–abdominal sites versus chest or head–neck sites (Slater, Ngo, & Lau, 1976). Considering chemotherapies, some will suppress lymphocyte proliferation, yet others are designed to enhance lymphocyte proliferation; but more typically, the immune-moderating effects of most chemotherapies are unknown. One of the more well-studied drugs (from an immune standpoint) is cyclophosphamide (CY). It consistently causes a sharp reduction in circulating peripheral blood lymphocytes and lymphoproliferative responses to mitogens, although the effect on antibody production is more variable (Ehrke, Mihich, Berd, & Mastrangelo, 1989). In contrast, CY can augment immunity to clinically relevant antigens; the leading hypothesis for how this occurs is that CY has selective toxicity for suppressor T cells or their precursors. Another drug, less well-studied from an immune standpoint, but one as widely used clinically, is adriamycin (ADM). The most prominent immunosuppressive effect of ADM is that it induces my elosuppression, which is likely due to the well-established antiproliferative effects of such anthracycline antibiotics. Although the immunopotentiation effects have not been studied as extensively, clinical studies with cancer patients have suggested that long-term ADM therapy does not appear to alter cell-mediated immunity, but data suggest that recovery is complete by one to three weeks after therapy (Kempf & Mitchell, 1984a, 1984b).

We acknowledge the complexity of these issues and suggest special care in the selection of stratification variables (see prior discussion) so that it might be possible to de facto equate groups on the heterogeneous treatment options that might be available for a single site of disease. Of course, full documentation of the nature of the regimens for subjects, including dosages and timing of delivery, is essential. In addition to following basic guidelines for behavioral immunology studies (Kiecolt-Glaser & Glaser, 1988a), investigators will need to consider strategies for controlling variation in blood draws for cancer patients; for example, scheduling blood draws before chemotherapy administration may maximize the likelihood of tapping recovered responses at the end of cycles rather than any acute dysregulation with drug administration per se. Multiple blood draws to monitor immunity after patients are off therapy will also be important. Unfortunately, contextual factors relevant to blood draws may also be important for chemotherapy patients. Data from Bovbjerg et al. (1990) suggest that psychological factors may operate for conditioned immune suppression following cytotoxic chemotherapy much as they do for other chemotherapy side effects, such as anticipatory nausea and vomiting.

Third, skeptics often note a related concern—the magnitude of change from psychological and behavioral factors that would be needed to affect immunity (or cancer progression) is unknown. We agree that such data are unavailable. However, the absence of this data is not unique to the PNI field but characterizes much of the basic research in immunology and cancer. For example, there are no such data linking changes in immune responses and disease progression for many of the current biological response modifiers (e.g., lymphokine-activated killer cells or interferons) being tested as cancer therapies. Immunotherapies are tested on the basis of their mechanisms at the level of the cell, and their effect on clinical outcomes (i.e., disease progression) is unknown but is seen as the relevant question to determine through clinical trials. The inability to specify the magnitude of change is not unique to this paradigm test for a psychological therapy, as the same criticism could be leveled against the testing of any new chemotherapeutic or chemopreventive agent. To illustrate, the current testing of Tomoxifen for breast cancer prevention is based on relevant but indirect lines of support. There is

experimental support that Tomoxifen affects both the initiation and promotion of tumors in animal studies, and it has lengthened disease-free survival and reduced the incidence of contralateral disease in women with breast cancer (Fisher, 1991; NSABP Protocol P-1). These data (and the fact that toxicity from Tomoxifen is low) were sufficiently encouraging to embark on a chemopreventive trial with 16,000 healthy women—even without two critical lines of evidence: (a) the precise mechanisms through which Tomoxifen achieves its effect are unknown and (b) there is only limited support for Tomoxifen's ability to increase survival rates in women with breast cancer (Fisher, 1991). Thus, it would seem unusual to hold tests of psychological therapies (which by their nature are nontoxic) to higher standards than the ones used for clinical trials of immunotherapies, new agents, or new uses of old agents.

Finally, a related methodologic concern is that the effects of stress on immune responses are small and are usually within normal ranges. We agree with this characterization, as it holds for the correlations with stress (Herbert & Cohen, 1993b), the psychological intervention studies (Kiecolt-Glaser & Glaser, 1992; Kiecolt-Glaser, Glaser, et al., 1985), and experimental studies of self-disclosure (Pennebaker, Kiecolt-Glaser, & Glaser, 1988) or relevant (personality) disclosure styles (Esterling, Antoni, Fletcher, Margulies, & Schneiderman, in press). But in all of these lines of research—research programs that use different paradigms, different subject populations, and documentation of psychological changes—the findings are consistent for the direction of the effect (i.e., immune downregulation with heightened distress) and for the effects to covary with experimental manipulation via psychological interventions or methods (e.g., ranging from brief self-disclosure for healthy individuals to eight-week interventions for cancer patients). Thus, although the immune effects are small, they are robust across samples and manipulations. Furthermore, these supportive findings include studies with cancer patients (Fawzy et al., 1990) and the same type of manipulations (Esterling et al., in press; Kiecolt-Glaser, Glaser, et al., 1985) that would be offered in psychological therapies.

Conclusion

Several studies have documented that quality of life benefits, such as reduced emotional distress, enhanced social adjustment, adaptive behavioral coping, symptom improvement (e.g., pain reduction or stabilization), and so forth, accrue from a psychosocial intervention offered to cancer patients. In contrast, health behaviors and compliance have rarely been intervention targets, although data suggest that such a broadened approach would be very effective. We view stress (quality of life), health behaviors, and compliance as the major factors in adjustment to the cancer stressor. Also, part of the biobehavioral model is the biological system, which may be one of the more important ones for moderating the effects of stress on disease processes, the immune system. The framework we have outlined addresses an important research need, as prior quality of life intervention studies have been in large part atheoretical. The proposed model endeavors to clarify the importance of psychological and behavioral factors for cancer patients and to clarify the routes by which such factors might have important health consequences.

Acknowledgments

We thank John T. Cacioppo and the reviewers for helpful comments.

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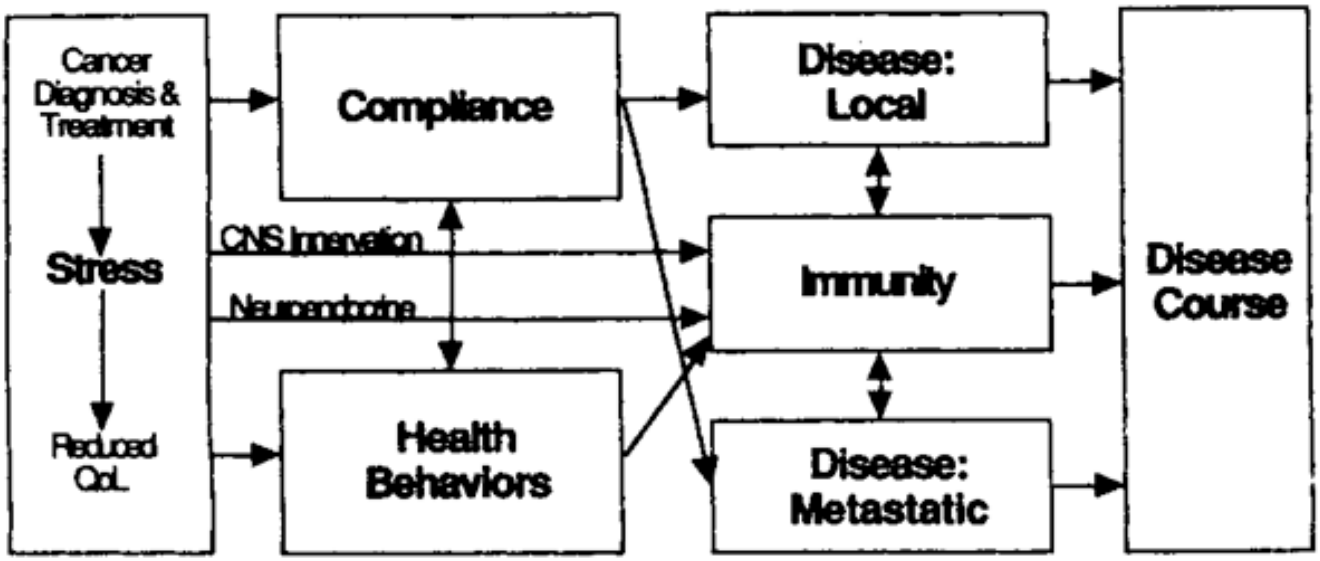

Figure 1.
A biobehavioral model of the psychological (stress and quality of life), behavioral (compliance and health behaviors), and biologic pathways from cancer stressors to disease course. CNS = central nervous system.

Table 1

5-year Survival Rates in Percentage for Selected Cancer Sites

	Extent of disease at diagnosis		
Site	**Localized**	**Regional**	**Distant**
Esophagus	22	7	1
Lung	47	14	1
Female breast	94	74	19
Cervix	90	53	13
Ovary	89	36	17
Prostate	93	83	29

Note. Adapted from Boring, Squires, Tong, and Montgomery (1994).