

*Stress and cancer: disorders of
communication, control, and
civilization*

Paul J. Rosch

*Whatever happens in the mind of man, is always
reflected in the diseases of his body.*

René Dubos

*The mind is its own place, and in itself,
Can make a heaven of hell, a hell of heaven.*

John Milton

Mind moves matter.

Virgil

In 1977, Hans Selye's International Institute of Stress cosponsored, with the Sloan Kettering Institute in New York, a symposium entitled "Cancer, Stress, and Death". Selye and I had developed a close friendship since my Fellowship at his Institute in 1951, when we coauthored articles dealing with his novel concepts.^{1, 2} Over the intervening years, he had invited me to prepare updated reviews, we corresponded frequently, and tried to meet when mutually convenient.^{3, 4} He had come to New York in connection with the symposium, and during dinner, indicated that he had a very personal interest in this subject. Five years previously, a tumor in his thigh was diagnosed as histiocytic reticulosarcoma, a normally fatal malignancy, from which he apparently completely recovered. He had refused chemotherapy, and attributed his good fortune not to any other treatment received, but rather his very firm determination to continue living so that he could complete his important research activities. Based on anecdotal reports of similar experiences and spontaneous remissions, he was convinced that a firm faith and fierce determination could retard or reverse cancer growth. Conversely, he wondered whether stress might contribute

to the development of certain malignancies, or accelerate their growth and metastases. He recalled that I had previously suggested that cancer might represent another of his "Diseases of Adaptation" and asked if I could contribute a paper that would support this. It was difficult for me to refuse anything that Selye requested, but I politely pointed out a variety of potential pitfalls in attempting to prove such a link. In addition, I had been completely involved in clinical practice for the past 20 years, and no longer had the time, training, or resources to adequately address this subject. We reminisced about other things, and I assumed the matter was closed.

Several weeks later, however, I received a large parcel, filled with an assortment of articles dealing with various pertinent experimental and clinical reports. It fortuitously arrived just before I was going on vacation, so I took it with me and had an opportunity to leisurely review its contents. Selye had written comments on many of the reprints to support his position, or questions designed to pique my curiosity. He also suggested that I contact various authorities concerning their opinion or experiences with respect to possible relationships between stress and cancer, but this did not prove very helpful. The President and Director of Sloan Kettering, which cosponsored the symposium, replied, "I have no information about stress and cancer," although he conceded that the topic was "most important".⁵ I found it fascinating, became increasingly inveigled by its possibilities and challenges, and eventually acquiesced.⁶

Since then, there has been an explosion of interest and articles on every aspect of this subject. Advances in our understanding of psychoneuroimmunologic relationships have also provided important insights that suggest possible mechanisms that could explain some anecdotal observations.^{7,8} Unfortunately, some pop psychologists and self-help zealots have gone overboard, by implying that certain types of cancer are usually stress related. Nothing could be crueler than adding to the stress and guilt of cancer patients, by insinuating that their illness, or failure to improve with treatment, is due to some deficiency in their character.⁹ Many of these claims confirm the questions and concerns I originally conveyed to Selye, and should be kept in mind when evaluating extravagant allegations. A "baker's dozen" of these caveats include:

1. How can we satisfactorily define "stress"?
2. How can we scientifically measure "stress"?
3. How can we define or distinguish between acute and chronic stress, since Selye had demonstrated they were so different in his General Adaptation Syndrome?
4. How can we ascertain when or where a malignancy first begins?
5. How can we determine the duration between initial onset and clinical detection?
6. Do all cancers share some common etiologic component?

7. How can we reconcile conflicting animal studies and clinical reports demonstrating that stress can both accelerate and retard malignant growth?
8. What are the mechanisms that might mediate relationships between stress and cancer?
9. What does "the immune system" consist of and where are its constituents located?
10. What are the best ways to measure immune system function, with respect to responses to stress and susceptibility to cancer?
11. While certain types of stress appeared to lower immune system measurements thought to reflect resistance to cancer (natural killer cell and T cell mitogenic activity), other stressors have an opposite effect.
12. Stress stimulates some endocrine responses that accelerate the growth of certain tumors, but also others that have inhibitory effects.
13. How can we explain the observation that all the interventions we use to treat cancer (radiation, hormones, and chemotherapy), also facilitate the development of malignancy?

The most obvious question is "What Is Stress?" There is still no satisfactory scientific definition, despite decades of attempts to decipher this dilemma.¹⁰ Stress is a useless term for pragmatic researchers, because it represents different things to different people, really is different for each of us, and most importantly, often cannot be measured with any significant degree of accuracy. Stress is used interchangeably to denote physical stressors, such as pain, noise, and opposite extremes of temperature, but also emotional states varying from depression and loneliness, to anxiety, anger, and hostility. Do all of these have common characteristics that are relevant to cancer?

Similarly, "What Is Cancer?" Although the term refers to undisciplined and uncontrollable cellular growth, a basal cell carcinoma of the skin is quite different from adenocarcinoma of the lung, prostate, or breast, brain tumors, lymphomas, leukemias, and other malignancies. These all differ markedly with respect to growth rates, metastatic tendencies, and sensitivity to neuroendocrine or immune system influences, particularly those that might be modulated by stress. There are critical concerns when it comes to determining exactly how long a cancer has been present. If a lump in the breast is found to be malignant, when did the cancer start? A month, six months, or years before clinical detection? Such information would be crucial to establish any temporal relationship with antecedent stress.

Even if we could confirm stress-induced neuroendocrine, immune system, or other pathways that induce malignant changes, this is not proof that stress can cause cancer. It is essential to emphasize that association never proves causation.¹¹ Although there are well-defined risk factors for certain malignancies, this simply signifies some statistical association,

rather than proving a causative, or even contributory, role.¹² However although it may never be possible to prove that stress can initiate or modify malignant growth, supportive evidence from different disciplines is impressive and compelling.¹³ Since space limitations preclude documenting all of these, ample supplemental references have been provided to supply additional information on specific topics.

Neurohumoral, immune, and subtle energy influences

Any attempt to explain how stress could affect malignant growth would have to demonstrate germane effects on systemic activities possessing this potential. There is abundant support with respect to immune, humoral, and central nervous system influences. These three integrative networks are intimately involved in regulating adaptive reactions to stress by surveillance of the status of specific parameters, and responding in an expedient and coordinated fashion.¹⁴⁻¹⁸ The numerous interactions between the central nervous and immune systems and their links to stress can be found in several reviews.¹⁹⁻²⁴ The hypothalamus plays a crucial role in mediating these as well as endocrine responses.²⁵⁻²⁸ Many brain neurotransmitters that can influence malignant growth also participate in the humoral response to stress, including melatonin, serotonin, dopamine, and the endorphins.²⁹⁻⁴⁰

Some types of cancer are very sensitive to hormonal influences. Estrogens, androgens, progestins, glucocorticoids, insulin-like growth factor, prolactin, and iodothyronines can directly modulate neoplastic growth, and influence other hormones that affect cancer cells.⁴¹⁻⁴³ Some of these actions may be direct, such as estrogen suppression of follicle stimulating hormone, whereas others influence hormonal binding or immune responses.⁴⁴⁻⁵⁰ Breast and prostate cancer are notoriously hormone dependent, and manipulating the hormonal environment is a cornerstone of treatment. Steroidal sex hormones can affect tumor growth factors and other immune system activities, and are sometimes used in the treatment of autoimmune disorders.⁵¹⁻⁵³ Stress profoundly effects key hypothalamic and pituitary peptides that regulate the activity of target endocrine glands that can modify tumor growth.⁵⁴

Glucocorticoids and their congeners dramatically influence the progression of leukemias and lymphomas, and levels produced in response to stress can provide similar clinical benefits. The composer Bela Bartok is often cited as an illustration. While dying in the terminal stages of advanced leukemia, he was approached by Serge Koussevitsky, the Conductor of the Boston Symphony Orchestra, who offered him a commission for a new work. He promptly went into an inexplicable remission, which persisted only until the composition had been completed, after which he promptly succumbed to the disease.⁵⁵ There are numerous other anecdotes similar to this which support Selye's contention about the ben-

efits of a firm faith and powerful purpose. It is doubtful that these are all mediated by increased glucocorticoid activity, but there are other possible explanations.

Lowered immune defenses clearly predispose to the development of malignancy, and conversely, heightened immune resistance is presumed to provide protection. Consequently, reports attempting to show some relationship between stress and cancer try to support this conclusion by demonstrating suppression or stimulation of "the immune system".^{56, 57} As noted, stress is a semantic snakepit for scientists, who also have concerns about categorizing different cancers as a collective entity with common characteristics. Similar confusion surrounds the immune system. There is an unfortunate tendency to assume that by giving something a name, we have now somehow defined it, and therefore agree on, or understand, what it means. Although the term is used freely and authoritatively, we have only a sketchy grasp of what the immune system comprises, or where each of its varied components is located. There is no distinct global measurement of immune system function. We can assess levels and ratios of T cells, B cells, helper cells, suppressor cells, natural killer cells, and responses to various blastogenic stimuli. We can measure specific immunoglobulins and antibodies in blood, saliva, urine, and cerebrospinal fluid, thymosin, interferons, interleukins, properdin, and other elements or markers. Humoral immune responses occur in minutes or seconds, whereas those that are cell mediated may not be evident for days and weeks. The same stressor might cause some immune measures to increase while others are simultaneously suppressed or unaffected. The nature of the stressor, its severity, duration, prior exposure, age, sex, race, nutritional considerations, health status, and hereditary factors may all influence immune responses that have been associated with cancer activity.⁵⁸⁻⁶¹ It is essential to consider such variables when evaluating claims about the effects of stress on "immune system function". Very divergent conclusions could be reached depending upon such modifiers, and which particular parameters of immune system function were selected.

In addition to central nervous system, humeral, and immune mechanisms, weak electromagnetic forces may also accelerate or depress malignant growth. Nordenström has postulated that there is an electrical circulatory system in the body.⁶² Based on this, he has developed an effective treatment program for lung and breast malignancies using very feeble electrical forces, and these impressive results have now been replicated in other centers.^{63, 64} Other investigators have now also confirmed that such energies, in conjunction with conventional therapy, can markedly retard or reverse head and neck cancers and brain tumors previously resistant to treatment.⁶⁵⁻⁶⁷ It is not inconceivable that similar subtle forces generated within the body may have comparable consequences that could explain spontaneous regression, as well as a variety of other reported relationships between stress and cancer. The concept that there may be psychoelectroneu-

roimmunologic responses has been proposed, and may be useful in exploring this possibility.⁶⁸

Historical support

The belief that stress could cause various diseases or influence their course has always been a popular notion. It can be found in all ancient religions and philosophies, and was emphasized in Ayurvedic principles and practices that have persisted for more than 3500 years.⁶⁹ The notion that cancer might in some way be related to emotional stress is as old as the history of recorded medicine. Cancer, is derived from *karkinos*, the Greek word for crab, which in Latin became "cancer". This apparently stemmed from the observation that the large veins surrounding a tumor resembled the claws of a crab, as evidenced by Galen's description:

As a crab is furnished with claws on both sides of the body, so in this disease the veins which extend from the tumor represent with it a figure much like a crab.

Four centuries later, Paul of Aegina suggested:

Cancer is so called because it adheres with such obstinacy to the part it seizes, that like the crab, it cannot be separated from it without great difficulty.⁷⁰

Middle English astronomers unfortunately used the term to describe the constellation between Leo the Lion and Gemini the Twins. Thus, the Tropic of Cancer marks the most northern latitude at which the sun can be seen directly overhead, usually at noon around June 22. Although the use of cancer in astrology has no connection with its medical meaning, some superstitious people still believe that anyone born under this Zodiac sign is more predisposed to die of cancer.

In his treatise on tumors, *De Tumoribus*, Galen observed that melancholy women were particularly prone to cancer of the reproductive organs because they had an excess of black bile (Gr. *mélas chole*). This may clarify why the earliest (1601) English definition explained that:

Cancer is a swelling or sore coming of melancholy blood, about which the veins appear of a blacke or swert colour spread in the manner of a creifish (crayfish) claws.

Galen believed that such humors, vital spirits, imagination, blood, muscle, and nerves were all closely linked with one another, in some hierarchical fashion. Thus, thoughts and feelings were constantly circulating through the body, exerting their effects by direct physical contact with par-

ticular parts of our anatomy. This was 2000 years before the development of psychoneuroimmunology as a discipline.

In 1701, the English physician Gendron emphasized the effect of "disasters of life as occasion much trouble and grief" in the causation of cancer.⁷¹ Eighty years later, Burrows attributed the disease to "the uneasy passions of the mind, with which the patient is strongly affected for a long time."⁷² Nunn was impressed with the influence of emotional factors on breast tumors,⁷³ and Stern similarly noted that cancer of the cervix in women was more common in sensitive and frustrated individuals.⁷⁴ In the mid-1800's, Walshe's *The Nature and Treatment of Cancer* called attention to

the influence of mental misery, sudden reverses of fortune and habitual gloomings of the temper on the disposition of carcinomatous matter. If systematic writers can be credited, these constitute the most powerful cause of disease.⁷⁵

Towards the end of the century in a study of more than 250 patients at the London Cancer Hospital, Snow concluded that "the loss of a near relative" was an important factor in the development of cancer of the breast and uterus.⁷⁶ Numerous additional citations attest to the firm belief of 18th- and 19th-century physicians that stressful states and emotions predisposed to cancer.⁷⁷⁻⁷⁹

I attach particular importance to these commentaries, because the practice of medicine in the last two centuries was quite different from today. This is particularly important with respect to patient encounters, which were much more personalized. Those physicians had to rely more upon eliciting and appraising the significance of the patient's history, environment, emotional makeup, and lifestyle, in contrast to contemporary diagnostic workups, which emphasize sophisticated laboratory tests and imaging procedures. Their education was much more apt to include a strong background in literature, philosophy, history, and other branches of learning concerned with human thought and relations, rather than the prevailing preoccupation with a basic science curriculum. They undoubtedly spent much more time observing patients, and talking to them about intimate family, social, and work relationships, and other potentially pertinent psychosocial influences. Thus, by virtue of educational enlightenment, cultural orientation, and a more personalized approach, they might well be expected to have had a greater sensitivity to any subtle relationships between stress and cancer, than is possible in the frenetic pace of today's high-tech, and often apathetic, practice environment.

Interest was rekindled in this subject in the 20th century with the advent of psychiatry as a specialty, and its emphasis on individual psychodynamics. Evans, a Jungian psychoanalyst, again called attention to the link between loss of a close emotional relationship and cancer.⁸⁰ Kissen

first noted that there appeared to be similar personality traits in patients with lung cancer that differentiated them from those with other pulmonary diseases, simply by taking a detailed personal history, and later extended these observations to other malignancies.⁸¹⁻⁸⁵ Schmale and Iker were intrigued with the relationship between antecedent stress and cancer of the cervix.⁸⁶ Merely by reviewing a personality questionnaire completed by asymptomatic women with suspicious pap smears, they were able to predict, with almost 75% accuracy, those who would subsequently develop cancer. Malignancy was most likely to surface in women with a "helplessness-prone personality" or overwhelming sense of frustration due to some emotional loss or conflict during the preceding six months, and this has recently been reconfirmed.⁸⁷⁻⁹⁰ Greene carefully studied the life histories of three sets of identical twins, one of whom had died of leukemia. He noted that each one with the disease had experienced an antecedent emotional upheaval not shared by the survivor.⁹¹ In another 15-year study of patients with lymphoma or leukemia, he found that the disease was more apt to occur following emotional loss or separation, which had engendered sustained feelings of anxiety, anger, sadness, or hopelessness.⁹²

Thomas's 40-year prospective health study of medical students was designed to determine whether there were any emotional patterns or stressful antecedents that might predict the development of hypertension in later life. It included a variety of psychological assessment techniques including figure drawing and extensive personal and family interviews. Follow up revealed that there were personality profiles not only for hypertension, but also suicide, mental illness, coronary heart disease and cancer.⁹³ Physicians who subsequently developed tumors often tended to be lonely individuals, who had figuratively "lost their parent", or had difficulties in adequately expressing their emotions.⁹⁴ Le Shan was impressed with similar characteristics seen in cancer patients, and particularly their possible contributory role.⁹⁵⁻⁹⁷ Based on a thorough review of the literature and more than two decades of detailed interviews, he concluded that there were four key types of personality characteristics that tended to precede the onset of malignancy:

1. The loss of an important emotional relationship
2. An inability to express anger or resentment
3. An unusual amount of self-dislike and distress
4. Feelings of hopelessness and helplessness.⁹⁸

The first item appears to be of particular importance. Various writers and poets have also emphasized this theme, including Tolstoy,⁹⁹ Auden,¹⁰⁰ and Sontag.¹⁰¹ Even the emotional loss of political defeat has been suggested as contributing to the cancers of Napoleon, Ulysses S. Grant, Robert Taft, Hubert Humphrey, and The Shah of Iran.¹⁰²

Animal research support

Animal studies have also demonstrated links between stress and cancer. Investigators in Pavlov's laboratory reported that dogs subjected to severe and chronic stress had a marked tendency to develop malignancies of the internal organs.¹⁰³ Riley studied a strain of mice carrying the Bittner mammary tumor virus. Under normal circumstances, 70 to 80% can be expected to develop breast cancer within one year. However, routine conditions in animal laboratories can be quite stressful, even in the absence of painful procedures. There is often unexpected and excessive noise, a confined environment, and frequent jarring movement of the racks holding the cages. Such animals have been shown to have much higher levels of stress-related hormones than others maintained under peaceful and quiet conditions. Exposure to pheromones that signal stressful states might also contribute to this. Riley found that when he protected these mice by placing them in protective housing that completely insulated them from all laboratory commotion and potentially stressful stimuli, only 7% had evidence of tumors at the end of a year. Conversely, the stress of simply periodically rotating litter mates on a turntable resulted in a 92% incidence of breast cancer.¹⁰⁴ The growth of transplanted mammary tumors can also be markedly increased by stressing experimental animals with electric shocks.¹⁰⁵⁻¹⁰⁷

Stress is an unavoidable consequence of life, but is most damaging when it is perceived to be completely beyond control. This is an important issue with respect to relationships with cancer, best illustrated by "yoked testing" experiments. In one such study, two matched groups of rats were housed in separated soundproof chambers and subjected to identical electrical shocks delivered in an erratic fashion with respect to time intervals and duration. When a rat in the first group depressed a small lever, it terminated the shock received by it. In the second group, pressing a similar lever did nothing. A third matched group, living under normal laboratory conditions, received no shocks, serving as controls to reflect normal tumor growth in the absence of this stressful stimulus. All of the animals were injected with a dosage of Walker²⁵⁶ sarcoma virus calculated to induce malignancies in 50% of recipients, to determine whether the physical stress of the shock could influence tumor growth. Three out of four rats in the second group, who received shocks over which they had no control, developed malignant tumors. As expected, the incidence of tumors was 50% in the non-shocked group of rats. However, in the first group of rats, who had received identical shocks as the second but were able to exert some control over them, tumors could be found in only one third. The rats in this group had less than half as many tumors as litter mates subjected to the same stress over which they had no control, and one third less than those who had received no shocks at all!¹⁰⁸

A "fighting attitude" can retard the development of experimental leukemia in mice, and transplanted mammary tumors in female mice who

spontaneously developed an antagonistic or fighting behavior, were also smaller and slower growing, than those in more submissive litter mates.¹⁰⁹ A similar phenomenon has been observed in "feisty" females with breast cancer.¹¹⁰⁻¹¹² This may have therapeutic implications, and again suggests that the feeling of being in control can inhibit malignant growth.^{113, 114} Other significant effects of stress on the development and growth of cancer in experimental animals have been summarized elsewhere.¹¹⁵ However, not all researchers agree. Some supportive animal and clinical studies have been criticized because of their design, failure to control for pertinent variables, and contrary findings with respect to results, or presumed mechanisms of action.¹¹⁶⁻¹²³

Personality and psychosocial stress as precursors to cancer

In addition to the historical citations noted, more recent reports are also replete with references linking stress and cancer. Depression is most frequently cited, and is supported by evidence of concomitant reduction of natural killer cell and other immune system activities.¹²⁴⁻¹²⁸ Feelings of helplessness, hopelessness, and suppression of emotions, particularly anger, may predispose to cancer.¹²⁹⁻¹³² Suppression of anger is associated with higher serum immune globulin-A levels, which have been shown to correlate with metastases and mortality rates in breast cancer.^{133, 134} Stress can also affect the metastatic spread of other tumors.¹³⁵⁻¹³⁸

Increased antecedent stress as assessed by the magnitude of life change events has been reported to be associated with a greater subsequent incidence of certain cancers.¹³⁹⁻¹⁴¹ The most stressful life change event is the death (loss) of a spouse, and significantly higher mortality rates for cancer and other leading causes of death have been reported in bereaved survivors over the following 6 to 12 months.¹⁴²⁻¹⁴⁴ Several studies have demonstrated concurrent impaired immune function, especially depression of T cell mitogenic and natural killer cell activity during this time period.¹⁴⁵⁻¹⁴⁸ The next three most stressful life change events, divorce, marital separation, and death of a close family member, also reflect emotional losses, and are similarly associated with higher cancer mortality rates.¹⁴⁹⁻¹⁵¹ Decreased immune defenses may accompany such losses, and can even be seen in workers who lose their job and remain unemployed.¹⁵²⁻¹⁵⁶ Psychosocial stresses such as poverty, social isolation, and low societal status, appear to be risk markers for malignancy.¹⁵⁷⁻¹⁶⁶ Conversely, the incidence of cancer appears to be unusually low in schizophrenic and certain other psychiatric patients, possibly because they do not consider such situations as stressful, or may be unable to experience the normal feelings and emotions associated with loss and separation.¹⁶⁷⁻¹⁷⁰

Various constellations of personality traits seem to be connected with increased cancer tendencies, and possibly predispose to behaviors and

lifestyles that are risk factors, or render individuals more susceptible to the effects of stressful life change events.¹⁷¹⁻¹⁸² So called "Type C" cancer-prone patients have been characterized as cooperative, conforming, compliant, and unassertive, with a tendency to suppress negative emotions, particularly anger.¹⁸³⁻¹⁸⁵ This characteristic of "pathological niceness" is commonly encountered in malignant melanoma, which is also often associated with increased antecedent stress.¹⁸⁶⁻¹⁸⁸

African antelopes and the teleology of evolution

The loss of important emotional relationships clearly constitutes the most stressful life change events. As emphasized above, they also represent the most common emotional and psychological precursors of cancer. Could there be some causal relationship between psychological loss and cancer? Implicit in Cannon's "fight or flight" theory is the teleological premise that our automatic and uncontrollable responses to stress have been steadily sharpened over the lengthy course of evolution. It is posited that they represent adaptive changes that were essential for the survival of our antedeluvian ancestors, when faced with life-threatening physical challenges. The outpouring of adrenalin and stimulation of the sympathetic nervous system resulted in pupillary dilatation to promote better vision, quickened clotting to reduce blood loss from lacerations or internal hemorrhage, a rise in blood pressure and heart rate to increase blood flow to the brain and facilitate decision making, increased blood sugar and lipid levels from the breakdown of carbohydrate and fat stores furnished more fuel for energy, and numerous other responses that were purposeful for primitive man. The shunting of blood flow away from the gut, where it was not immediately needed for digestive purposes, to the large muscles of the arms and legs; provided greater strength for fight in combat, or flight from a scene of potential peril.

However the nature of stress for modern man is not some physical encounter with a saber toothed tiger or warring tribe every few months but rather an array of psychological and emotional threats and challenges which may occur several times daily. The tragedy is that these trigger automatic, archaic, "fight or flight" responses, which are no longer purposeful or appropriate. Repeatedly invoked, it is not difficult to understand how they could contribute to such "Diseases of Civilization" as hypertension, diabetes, heart attack, stroke, peptic ulcer, muscle spasm etc. Many of our responses to stress seem senseless, and it may be difficult to appreciate how they could ever have been beneficial. When severely frightened, some people feel their "flesh crawl", develop "goose bumps", or the hairs on the back of the neck "stand up". Although all of these are useless for us the "flying fur" on the arched back of an aroused cat makes it appear more ferocious to an assailant. Similarly, the stimulation of those same arrector pili muscles is responsible for the "bristling quills" of the porcupine,

which is a very effective defense mechanism. Thus, all of our instantaneous, instinctive, reflexive responses to stress undoubtedly served some useful purpose during the lengthy course of human evolution. It is equally apparent that we may often overreact to a stressful stimulus with healing consequences that prove harmful. We see this in the occasional development of disfiguring keloids due to excessive scar formation, and when lip cancer develops in clay pipe smokers, in an attempt to repair heat-damaged tissue.

There are other instances where adaptational evolutionary responses may ultimately prove pernicious. In a review article on Selye's concepts of "Stress" and "Diseases of Adaptation" over 33 years ago, I referred to the theory of "opportunism" in the evolutionary process. This refers to the organism's response to fill a need with whatever means are available, even if the long-term consequences proved undesirable. The illustration cited at that time was the tremendous variation in the development of distinctive horns by some 23 species of African antelopes. The horns of the kudu are prohibitively unwieldy, while those of the duiker are obviously too small to be effective. As one examines the different deviations that have evolved in others, their divergent anatomical configurations and functional capabilities do not appear to serve any rational adaptive purpose. If I were to rewrite that article today, I would choose the development of malignancy in man as perhaps a more dramatic example of "opportunism" in the evolutionary process, for the following reasons.

As one descends the phylogenetic scale, the incidence of malignancy decreases progressively. Cancer does not occur in primitive forms of life. Conversely, the ability of the organism to regenerate injured or lost tissues increases proportionately. Simple organisms, including some invertebrates, have the ability to sever parts of their anatomy when they are injured. This capability would have survival value only if the animal possessed an equally remarkable ability to regenerate the cast off portion from available cell remnants. A starfish can restore a lost appendage, and the newt will grow a new tail or leg if it is severed, or can even cause its mechanical release to escape a predator. This restorative capability is not retained in humans, although the spleen does possess unusual regenerative potential.

I believe that some malignant responses in man may represent an atavistic, vestigial remnant of this primordial, purposeful, regenerative trait. When we suffer a loss or injury, attempts at replacement could well be activated, as they are in lower life forms. Unfortunately, this new growth (neoplasia) may prove to be harmful rather than helpful. Experiments with chemicals that cause cancer when applied to the human skin or injected into rodents support this hypothesis. When these same carcinogens are injected into the leg of a newt, a new accessory limb starts to grow at that site, rather than a tumor. If injected into the epithelial iris tissue of the eye, the newt will regenerate a new lens. Thus, the identical carcinogenic stim-

ulus can produce either purposeful regeneration or a malignant growth, depending upon the evolutionary development of the organism.¹⁸⁹⁻¹⁹²

It is interesting that the sole exception to this in humans is the spleen. Years after its surgical removal, remnants of functioning splenic tissue are often found, a phenomenon that has been referred to as the "born again spleen".¹⁹³ The spleen is also the only organ in humans that does not give rise to spontaneous cancer, suggesting that its response to loss has been preserved as purposeful regeneration. Small accessory spleens, or splenuli, are not uncommon, and in rare cases, several hundred may be present in or around the gastrointestinal tract. This represents a reversion to a more primitive condition, in which splenic tissue is not located in a single organ, but instead is scattered throughout the gut. Thus, from the standpoint of embryology and comparative anatomy, the spleen retains certain ancient attributes that may explain its unique freedom from cancer, as well as its remarkable regenerative capacity.

The leap from physical to emotional loss should not be too troublesome. The ability to regenerate lost or injured tissue in lower forms of life obviously involves something more than a simple local response. The message that tissue has been lost, irritated, or damaged must be relayed to higher centers in the central nervous system. These could initiate coordinated restorative activities, most likely involving the integration of central nervous system, humoral, and immune system mechanisms. With man's highly developed cerebral cortex, emotional loss may well be perceived as being an equally significant or even greater stress than physical privation. The same reparative signals may be activated, but our responses are anomalous and aberrant. Our strivings to stimulate purposeful replacement are futile and fruitless, and any resultant new growth is apt to be in the form of malignant neoplasia.

Selye was unusually enthusiastic about this theory, and emphasized it and associated concepts in his Foreword to *Cancer, Stress and Death*:

Perhaps, as Paul Rosch of New York has suggested, cancer might even be an attempt by the human organism to regenerate tissues and organs and even limbs, as lower animals are able to do spontaneously. Going further, one might say that "the ultimate health of the organism, like that of society, appears to depend on how well or appropriately its constituent units communicate with one another."¹⁹⁴

Cancer and civilization

In keeping with Selye's assignment, the title of my paper was "Stress and Cancer: A Disease of Adaptation?". In retrospect, "A Disease of Civilization" might have been a more appropriate subtitle. This may sug-

gest some allusion to smoking, air pollution, the proliferation of putative cancer-causing substances such as asbestos, depletion of the ozone layer, radiation hazards, or other current carcinogenic concerns. However, what I wish to refer to are psychosocial stresses that were evident long before these 20th-century problems. This concept is not new, and was proposed over 150 years ago in Tanchou's 1843 "*Memoir on the Frequency of Cancer*" delivered to the French Academy of Sciences:

M. Tanchou is of the opinion that cancer, like insanity, increases in a direct ratio to the civilization of the country and of the people. And it is certainly a remarkable circumstance, doubtless in no small degree flattering to the vanity of the French *savant*, that the average mortality rate from cancer in Paris during 11 years is about 0.80 per 1000 living annually, while it is only 0.20 in London! Estimating the intensity of civilization by these data, it clearly follows that Paris is four times more civilized than London!¹⁹⁵

Bainbridge's *The Cancer Problem*, noted:

Man in his primeval condition has been thought to be very little subject to new growth, particularly to those of a malignant character. With changed environment, it is claimed by some, there came an increase in susceptibility to cancerous disease, this susceptibility becoming more marked as civilization develops.¹⁹⁶

Hoffmann's treatise *The Mortality of Cancer Throughout the World*, a global survey conducted under the auspices of the Prudential Life Insurance Company, emphasized:

The rarity of cancer among native races (primitive races) suggests that the disease is primarily induced by the conditions and methods of living which typify our modern civilization. . . . A large number of medical missionaries and other trained medical observers, living for years among native races throughout the world, would long ago have provided a more substantial basis of fact regarding the frequency of occurrence of malignant disease among the so-called uncivilized races, if cancer were met with among them to anything like the degree common to practi-

cally all civilized countries. Quite the contrary, the negative evidence is convincing that, in the opinion of qualified medical observers, cancer is exceptionally rare among the primitive peoples including the North American Indians and the Eskimo population of Labrador and Alaska.¹⁹⁷

This was substantiated by the African medical missionary, Dr. Albert Schweizer:

On my arrival in Gabon in 1913, I was astonished to encounter no cases of cancer. I cannot, of course, say positively that there was no cancer at all; but like other frontier doctors, I can only say that if any cases existed, they must have been quite rare. In the course of the years, we have seen cases of cancer in growing numbers in our region. My observations incline me to attribute this to the fact that the natives are living more and more after the manner of the whites.¹⁹⁸

Similarly, the celebrated anthropologist and Arctic explorer, Vilhjalmur Stefansson, in his book which actually was titled *Cancer: Disease of Civilization?*, noted the absence of cancer in the Eskimos upon his arrival in the Arctic, but a subsequent increase in the incidence of the disease as closer contact with white civilization was established.¹⁹⁹ He quoted Sir Robert McCarrison, a physician who had studied 11,000 Hunza natives in Kashmir from 1904 to 1911. They not only enjoyed unusual longevity, but preserved their youthful physique and appearance well into their sixties and seventies. McCarrison attributed the absence of cancer to the fact that they were "endowed with a nervous system of notable stability" (resistant to stress), and "far removed from the refinement of civilization".

Hay's *Cancer: A Disease of Either Election or Ignorance*, commented:

A study of the distribution of cancer, among the races of the entire earth, shows a cancer ratio in about proportion to which civilization living predominates; so evidently something inherent in the habits of civilization is responsible for the difference of cancer incidence compared with the uncivilized races and tribes. Climate has nothing to do with this difference, as witness the fact that tribes living naturally will show a complete absence until mixture with more civilization, even so does cancer begin to show its head.²⁰⁰

In *Malignancy and Evolution*, Roberts wrote, "I take the view commonly held that, whatever its origin, cancer is very largely a disease of civilization".²⁰¹ He was referring to opinions such as those expressed in Moore's *The Antecedents of Cancer*, that "connect the progress of civilization with the increase of cancer which has remained an incontestable theory to the present day"; Banks' contention that "cancer is on the increase in this country. Is it possible that this is coincident with our full habit of living as a people?"; Powell's *The Pathology of Cancer*: "There can be little doubt that the various influences grouped under the title of civilization play a part in producing a tendency to Cancer"; and Hooker's *Eclecticism in Cancer Therapy*, which urged less emphasis upon research in artificially induced cancer in laboratory animals, and more emphasis upon the observation of people:

There is, as a matter of fact, a growing group of independent thinkers both lay and professional, who are anything but impressed with the story of the discovery and isolation of the "cancer germ". Mr. Ellis Barker has also written reiterating his views, in common with those of Sir William Arbuthnot Lane, my own and many others, that cancer is a disease of civilization.^{202, 203}

One of the most persuasive arguments is to be found in Berglas' *Cancer; Its Nature, Cause and Cure*. Throughout this book runs the theme that cancer is a disease from which primitive peoples are relatively or wholly free, and that we are

threatened with death from cancer because of our inability to adapt to present day living conditions . . . Over the years/ cancer research has become the domain of specialists in various fields. Despite the outstanding contributions of scientists, we have been getting farther away from our goal, the curing of cancer. This specialized work, and the knowledge gained through the study of individual processes, has had the peculiar result of becoming an obstacle to the whole. More than thirty years in the field of cancer research have convinced me that it is not to our advantage to continue along this road of detailed analysis. I have come to the conclusion that cancer may perhaps be just another intelligible natural process whose cause is to be found in our environment and mode of life.²⁰⁴

In addition to cancer, simple and stable societies are relatively resistant to diabetes, hypertension, peptic ulcer, and other "Diseases of Civilization". However, as Donnison reported in *Civilization and Disease*, this resistance is rapidly lost when established norms and traditions are swept aside by the pressures of civilization.²⁰⁵ Since the advent of Cro-Magnon, societal groups have progressively increased in size, and changed dramatically with respect to interpersonal relationships and values. Appropriate adaptive alterations have not kept pace with these evolutionary advances with respect to the acquisition of psychological and emotional assets that could facilitate acclimatization to swiftly shifting sociocultural environments.²⁰⁶ "Social disruption" may also increase susceptibility to tuberculosis and other infectious diseases.²⁰⁷ It is the rapidity of change which particularly predisposes to inappropriate and damaging coping responses that eventually result in reduced resistance to both physical and emotional disorders.^{208, 209}

Recent government statistics show a puzzling increase in the incidence of breast cancer in middle-aged females, which may also be related to certain new stresses of "civilization". It has been well established that the younger a woman is when she has her first child or even becomes pregnant, the less likely she is to develop breast cancer. Pregnancy lowers prolactin which stimulates breast tissue growth and promotes breast cancer in experimental animals. As more and more women enter the workforce, they tend to remain single, marry later in life, and decide not to have children or do so only when they are much older. Similarly, the incidence of deadly ovarian cancer is 14 times higher in career-oriented, single working women, compared to a matched group of homemakers. Job stress itself may be a factor, as many women workers have to juggle job responsibilities with being a wife, supermom, single parent, or providing custodial duties for an aged relative. Superimposed on this, there may be sexual harassment, lower compensation than male counterparts despite superior ability and experience, and a dead end when they try to reach the upper rungs of the corporate ladder.

Other demographic groups, including children, adolescents and the elderly are subjected to unique stresses not experienced generations ago, as a consequence of changes imposed by the pressures of contemporary civilization. Key among these are the rapid sociocultural changes that have eroded close family and religious ties, and the sense of belonging, so deftly described by Wolf in his studies of Roseto.^{210, 211} These also represent loss of meaningful emotional relationships that may not be fully appreciated, because they are not sudden and dramatic detachments. For today's younger generations, social ties are more often apt to lie in rooting for the same sports team, or being a fan of some rock group, or celebrity, rather than religion, family, or humane and redeeming relationships which are oriented towards, and have the capacity to relieve loss and suffering.

Biopsychosocioecological communication, control, and subtle energies

Similarly, civilization also seems to have been responsible for a progressive loss of communication with the cosmos, or nature. Life on earth consists of a hierarchy of living systems that range upward from atoms, molecules, cells, and organs, to people, families, corporations, and societies.²¹² Poorly understood communication channels continually connect all these components, as meaningful messages are sent up and down the line. Homeostasis and health are entirely dependent on good communication—good communication not only within the constituency of the internal environment of each system, but also with the external environment at higher and lower levels (Figure 1). These dynamic interrelationships are essential for the preservation of balance, harmony, and homeostasis in the universe. Such a biopsychosocioecologic perspective must be appreciated to comprehend the complex connections between psychosocial stress and cancer.

As Yamasaki has elegantly demonstrated, the basic problem with the cancer cell is that it no longer communicates properly:

Cancer can be regarded as a rebellion in an orderly society of cells when they neglect their neighbors and grow autonomously over surrounding normal cells. Since intercellular communication plays an important role in maintaining an orderly society, it must be disturbed in the process of carcinogenesis. Evidence suggests that blockage of intercellular communication is important in the promotion process of carcinogenesis.²¹³

Selye had previously described this need for cooperative communication in more humanistic terms:

The indispensability of this disciplined, orderly mutual cooperation is best illustrated by its opposite—the development of a cancer, whose most characteristic feature is that it cares only for itself.¹⁹⁴

But how does communication take place in the body? The nervous system communicates by direct contact, as adrenergic or cholinergic molecules are released at nerve endings and synapses. Endocrine secretions and neurotransmitter secretions are carried via the bloodstream to selected receptor sites on cell walls at distant locations. Much less is known about the immune system, although it is clear that its conversations include both humoral and hard wired connections. However, in the final analysis, all of these messages are transmitted by means of weak energy transfers across

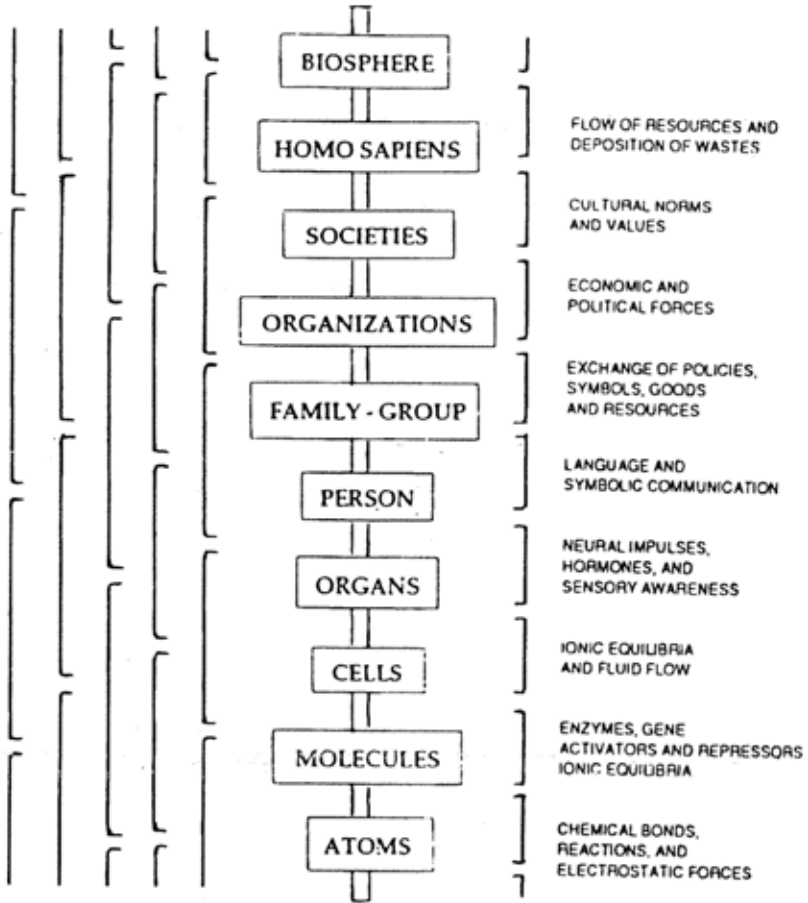


Figure 1 Information flow in hierarchial living systems.

cell membranes. These occur at an atomic rather than a molecular level. It has also become increasingly apparent that the cell membrane is more than a protective shield studded with receptor sites for antibodies, small neuropeptides, and other molecules. It appears to be a powerful signal amplifier that provides an interactive window through which the cell senses and responds to its environment. Some substances can pass freely back and forth through certain channels, but for others, the cell membrane is an impenetrable barrier. When designated molecules fit into special receptor sites, a subtle signal produces a sudden change in electrical tension between the interior and exterior of the cell, allowing a new channel to open for a few thousandths of a second. During this period, although millions of ions pass back and forth, the total current generated is only a few billionths of an ampere!

As previously proposed, I believe that cell membranes may have receptor sites for subtle energy signals which react exactly as they would to chemical/molecular stimuli. Electrical stimulation of highly specific areas in the pain pathway produces analgesia, and microinjections of morphine at these precise sites have the identical effect. Injection or stimulation a few millimeters away is worthless. However, combining suboptimal doses of morphine or electrical stimulation, which alone are too weak to reduce pain, results in a synergistic effect that does provide analgesia. This suggests that for some receptors, the effects of weak electrical stimulation are completely congruent with those of morphine. Furthermore, the specific locations at which either molecular or electrical signals relieve pain are precisely the sites of action of the endorphins.²¹⁴

If feeble electrical forces can produce such profound physiologic effects, this might account for the association of malignancy with proximity to high power lines, increased birth defects when electric blankets are used during pregnancy, and a variety of psychophysiological effects due to geomagnetic influences, including cancer.²¹⁵ Such observations cannot be explained in terms of Newtonian physics, or any form of chemical/molecular communication. It is quite likely that energies of similar magnitude can be generated in the body, that could also affect cell growth and malignant change. Electroencephalogram (EEG) waves may reflect more than the noise of the machinery of the brain, and possibly represent signals being sent to other parts of the body. Since it is possible to move a cursor on a computer screen solely by deep concentration, it does not seem unreasonable to postulate that mental activities could also affect activities in the body that are sensitive to rent chemical/molecular concept of communication, to a physical/atomic model. Such a paradigm might explain not only regression or spontaneous remission of cancer in patients with a strong determination, but also the placebo effect, faith healing, "therapeutic touch", psychokinesis, telepathic and other widely acknowledged, but poorly understood, phenomena.

Pribram²¹⁶ and Bohm²¹⁷ propose that the universe consists of swirls of energy fields that operate in dimensions far beyond our conventional senses. They view the brain as a holographic instrument which mathematically constructs concrete realities, by interpreting these energies from another dimension that transcends our current comprehension of time and space. A similar concept was expressed by William Wordsworth in his *Ode On The Intimations Of Immortality From Recollections Of Early Childhood*, and in recent years, Sheldrake has provided some scientific support for such beliefs.²¹⁸ The Chinese conceptualization of "chi" energy, and its role in health and disease has persisted for thousands of years, and is increasingly attracting scientific interest and support. However, *chi* is not only an energy system that flows through acupuncture meridians in the body, but is found in trees, rocks, and all of nature. Hence, the need to add an ecological component to our current biopsychosocial model of health.

Although we cannot define stress, all of our research confirms that the sense of being out of control is always distressful. That also happens to be an accurate definition of the cancer cell. It is a cell that is out of control, because it does not communicate properly with its neighbors, or the rest of the organism. A domineering and dogmatic determination, firm and forceful faith, and aggressive attitude, all reflect the development of a strong sense of control. These are common themes in reports of patients who triumphed over seemingly fatal malignancies.²¹⁹⁻²²¹ Can this message of control be communicated to cancer cells through unsuspected energy pathways to alter their undisciplined activities? Is it possible to listen in on this conversation? If we understood its vocabulary, could we learn how to emulate, simulate, or stimulate such subtle signals, and to utilize our innate and awesome potential for self-healing?

How can one explain the numerous well-documented cases of spontaneous remission of cancer? Careful studies of such patients suggest that a firm faith and a strong positive belief system is the most common denominator.^{222, 223} Anecdotal, but irrefutable, reports of cancer cures from shrines, faith healers, laetrile®, coffee enemas, acupuncture, macrobiotic diets, and other alternative treatments are difficult to explain. There are numerous reports of cancer regression through the use of various stress reduction or mind altering techniques, including intense meditation, visual imagery, and hypnosis.²²⁴⁻²³⁵ Yet, like spontaneous remission, all these cures are extremely rare, and benefits are entirely unpredictable in any given patient. Here again, having a strong faith in anything the individual believes in, and which provides a sense of control, might offer the best explanation. But how are the salutary rewards of faith healing, "therapeutic touch", and the placebo effect mediated? Is there such a thing as psychic healing? How can one explain the well-documented benefits associated with the development of strong social support in patients with cancer and other problems?²³⁶⁻²⁴¹ Conversely, what are the mechanisms involved in the numerous reports of reactivation of dormant cancer following an extremely stressful event, particularly sudden loss?²⁴²⁻²⁴⁵ No consistent immune, neuroendocrine, or central nervous system changes have been demonstrated in connection with such effects.^{246, 247} Could the answer lie in some latent energy force? Is it possible to learn how to harness this?

The endemiology of cancer

We are exposed daily to a host of potential physical carcinogens in the air we breathe or the foods we eat. However, not all smokers develop lung cancer, which also occurs in nonsmokers without any family history of malignancy or other conceivable contributory factor. I would suggest that there may be equally powerful psychosocial carcinogens that exist both in our external and internal milieus. Our current focus is on the epidemi-

ology of cancer, the roots of which connote some external stressor that the individual has been subjected to. What we must now also acknowledge is what might be referred to as the endemiology of cancer, and those factors that influence health which are generated in our internal environment.²⁴⁸

Good health is entirely dependent on maintaining the constancy or stability of the internal environment during stress. Walter Cannon coined the term "homeostasis", from the Greek *homios* (similar), and *stasis* (position), to refer to this "steady state".²⁴⁹ However, the concept of the importance of the internal environment, and the term itself (*milieu intérieur*) originated a half century earlier with the celebrated French physiologist, Claude Bernard,²⁵⁰ often called "The Father of Physiology". Louis Pasteur was a powerful proponent of external causes of disease, because of his discovery of pathogenic bacteria. He engaged in many debates about this with Claude Bernard at the prestigious *Académie Française*, where they sat next to one another. However, on his deathbed, Pasteur allegedly stated "*Bernard avait raison. Le germe n'est rien, c'est le terrain qui est tout.*" [Bernard was right. The microbe is nothing, the soil is everything.]²⁵¹

Sir William Osler reported the spontaneous shrinkage of metastases from breast cancer in two women in 1901.²⁵² It is interesting that the term "spontaneous" is so often used to describe this phenomenon, rather than "unexplained". Spontaneous refers to occurrences that happen without apparent external cause, and are therefore self-generated, as in "spontaneous combustion". Osler often commented that it was more important to know what went on in a patient's head than in his chest, to determine the clinical course of tuberculosis. He also paraphrased Parry's perception that "It is much more important to know what sort of a patient has a disease, than what sort of a disease the patient has."^{253, 254} This observation, as well as the important role of stress, is being increasingly confirmed in patients with hypertension, coronary heart disease, peptic ulcer, allergic conditions, psoriasis, low back pain, and a variety of mental and emotional disorders. As suggested in this presentation, it may be appropriate to insert cancer near the top of this list of "Diseases of Civilization".

References

1. Selye, H. and Rosch, P. J., Integration of endocrinology, in *Glandular Physiology and Therapy*, J. B. Lippincott, Philadelphia, 1946, 1-100.
2. Selye, H. and Rosch, P. J., The renaissance in endocrinology, in *Medicine and Science*, International University Press, New York, 1954, 30-49.
3. Rosch, P. J., Growth and development of the stress concept and its significance in clinical medicine, in *Modern Trends in Endocrinology*, Hoeber, P. B., Ed., Butterworths, London, 1958, 278-297.
4. Rosch, P. J., Stress: its relationship with illness, in *Traumatic Medicine and Surgery For the Attorney*, III, part 6, Cantor, P.D., Ed., Butterworths, Washington, D.C, 1960, 261-364.

5. Good, R., A., personal communication.
6. Rosch, P. J., Stress and cancer: a disease of adaptation?, in *Cancer, Stress, and Death*, Tache, J., Selye, H., and Day, S. B., Eds., Plenum Publishing, New York, 1979, 187-212.
7. Ader, R., Felten, D. L., and Cohen, N., Eds., *Psychoneuroimmunology*, Academic Press, San Diego, 1991.
8. Herbert, T. B. and Cohen, S., Stress and immunity in humans: a meta-analytic review, *Ann. Behav. Med.*, 55, 364-379, 1993.
9. Rosch, P. J., Mind over cancer: some caveats, *Stress Med.*, 10, 71, 1994.
10. Solve, H., Forty years of stress research: principal remaining problems and misconceptions, *Can. Med. Assoc. J.*, 115, 53-56, 1976.
11. Rosch, P. J., Stress, cholesterol, and coronary heart disease, *Lancet*, ii, 851-852, 1983.
12. Rosch, P. J., Ridiculous risk factors and heart attacks: diet-cholesterol dogma versus stress, *Stress Med.*, 9, 203-205, 1993.
13. Pettingale, K. W., Towards a psychobiologic model of cancer: biological considerations, *Soc. Sci. Med.*, 20, 779-787, 1985.
14. Bulloch, K., Neuroendocrine-immune circuitry: pathways involved with the induction and persistence of humoral immunity, *Diss. Abstr. Int.*, 41, 4447-B, 1981.
15. Stein, M., Stress, brain and immune function, *Gerontologist*, 22, 203, 1982.
16. Besedovskv, H. O. and Sorkin, E., Network of immune-neuroendocrine interactions, *Clin. Exp. Immunol.*, 27, 1-12, 1977.
17. Besedovskv, H. O. and Sorkin, E., Network of immune-neuroendocrine interactions, in *Hormonal Control of Immune Processes*, James, V. H. T., Ed., Oxford University Press, Amsterdam, 1977, 504-513.
18. Rosch, P. J., Illness syndromes: high disability, in *Psychiatry in the Medical Specialties*, Dunbar, F., Ed., McGraw-Hill, New York, 1959, 152-317.
19. Felten, D. L., Cohen, N., Ader, R., Felten, S. E., Carlson, S. L., and Rozman, T. L., Central neural circuits involved in neural-immune interactions, in *Psychoneuroimmunology*, Ader, R., Felten, D. L., and Cohen, N., Eds., Academic Press, San Diego, CA, 1991, 3-18.
20. Holland, J. C., Behavioral and psychosocial risk factors in cancer: human studies, in *Handbook of Psychooncology*, Holland, J. C. and Rowland, J. H., Eds., Oxford University Press, New York, 1989, 612-627.
21. Kiecolt-Glaser, J. K., Garner, W., Speicher, C. et al., Psychosocial modifiers of immune competence in medical students, *Psychosom. Med.*, 46, 7-14, 1984.
22. Kiecolt-Glaser, J. K., Glaser, R., Strain, E. C. et al., Modulation of cellular immunity in medical students, *J. Behav. Med.*, 9, 5-21, 1986.
23. Glaser, R., Rice, J., Stout, J. C., Speicher, C. E., and Kiecolt-Glaser, J. K., Stress depresses interferon production by leukocytes concomitant with a decrease in natural killer cell activity, *J. Behav. Neurosci.*, 100, 675-678, 1986.
24. Bardos, P., Biziere, K., DeGenne, D., and Renoux, G., Regulation of natural killer activity by the cerebral neocortex, in *Natural Killers: Fundamental Aspects and Role in Cancer*, Serron, B. and Herberman, R. B., Eds., Elsevier, Amsterdam, 1983, 346-359.
25. Stein, M., Keller, S., and Schleifer, S., Role of the hypothalamus in mediating stress effects on the immune system, in *Mind and Cancer Prognosis*, Stoll, B. A., Ed., John Wiley & Sons, New York, 1979.

26. S. Keller, S. E. et al., Suppression of lymphocyte stimulation by anterior hypothalamic lesions in the guinea pig, *Cell. Immunol.*, 52, 334-340, 1980.
27. Besedovsky, H. O., Sorkin, E., Felix, D., and Haas, H., Hypothalamic changes during the immune response, *Eur. J. Immunol.*, 7, 323-325, 1977.
28. Cross, R. J., Markesbery, W. R., Brooks, W. H., and Rozman, T. L., Hypothalamic-immune interactions. The acute effect of anterior hypothalamic lesions on the immune response, *Brain Res.*, 196, 79-87, 1980.
29. Lippman, M. E., Yarbrow, G. K., and Leventhal, B. G., Effects of glucocorticoids on F_c receptors of a human granulocyte cell line, *Cancer Res.*, 38, 4251-4256, 1978.
30. Heijnen, C. J., Kavelaars, A., and Ballieux, R., Corticotropin-releasing hormone and proopiomelanocortin-derived peptides in modulation of immune function, in *Psychoneuroimmunology*, 2nd ed., Ader, R., Felten, D. L., and Cohen, N., Eds., Academic Press, San Diego, CA, 1991, 429-446.
31. Irwin, M. R., Vale, W., and Britton, K. T., Central corticotropin-releasing factor suppresses natural killer cytotoxicity, *Brain Behav. Immun.*, 1, 81-87, 1987.
32. Irwin, M. R., Hauger, R. L., Brown, M. R., and Britton, K. T., CRF activates autonomic nervous system and reduces natural killer cytotoxicity, *Am. J. Physiol.*, 255, R744-R747, 1988.
33. Irwin, M., Brain corticotropin-releasing hormone- and interleukin-1 beta-induced suppression of specific antibody production, *Endocrinology*, 133, 1352-1360, 1993.
34. Irwin, M., Hauger, R., and Brown, M., Central corticotropin-releasing hormone activates the sympathetic nervous system and reduces immune function: increased responsivity of the aged rat, *Endocrinology*, 131, 1047-1053, 1992.
35. Johnson, H. M., Smith, E. M., Torres, B. A., and Blalock, J. E., Regulation of the *in vitro* antibody response by neuroendocrine hormones, *Proc. Natl. Acad. Sci. U.S.A.*, 79, 4171-4174, 1982.
36. Ben-Eliyahu, S., Yirmiya, R., Shavit, Y., and Liebeskind, J. C., Stress-induced suppression of natural killer cell cytotoxicity in the rat: a naltrexone-insensitive paradigm, *Behav. Neurosci.*, 104, 235-238, 1990.
37. Yirmiya, R., Shavit, Y., Ben-Eliyahu, S., Gale, R. P., Liebeskind, J. C., Taylor, A. N., and Weiner, H., Modulation of immunity and neoplasia by neuropeptides released by stressors, in *Stress, Neuropeptides, and Systemic Disease*, McCubbin, J. A., Kaufmann, P. G., and Nemeroff, C. B., Eds., Academic Press, San Diego, CA, 1991, 261-279.
38. Zagon, I. S. and McLaughlin, P. J., Endogenous opioid systems, stress and cancer, in *Enkephalins and Endorphins: Stress and the Immune System*, Plotnikoff, N. P., Faith, R. E., Murgu, A. J., and Good, R. A., Eds., Plenum, New York, 1986, 81-100.
39. Lapin, V., Pineal influences on tumor, *Prog. Brain Res.*, 52, 523-533, 1979.
40. Dilman, V. M., Anisimov, V. N., Ostroumova, M. N., Morozov, V. G., Khavinson, V. K., and Azarova, M. A., Study of the anti-tumor effect of polypeptide pineal extract, *Oncology*, 36, 274-280, 1979.
41. Lippman, M. E., Yarbrow, G. K., and Leventhal, B. G., Effects of glucocorticoids on F_c receptors of a human granulocyte cell line, *Cancer Research*, 38, 4251-4256, 1978.

42. Lippman, M. E., Endocrine responsive cancers in man, in *Textbook of Endocrinology*, Williams, R., Ed., W. B. Saunders, Philadelphia, 1985, 286-302.
43. Lippman, M. E., Strobl, J., and Allegra, J. C., Effects of hormones in human breast cancers cells in tissue culture, in *Cell Biology of Breast Cancer*, McGrath, C., Brennan, M., and Rich, M., Eds., Academic Press, Orlando, FL, 1980, 218-234.
44. Kakidani, H. et al., Cloning and sequence analysis of cDNA for porcine B-neo-endorphin/dymorphin precursor, *Nature*, 298, 245-249, 1982.
45. Berczi, I. and Nagy, E., A possible role of prolactin in adjuvant arthritis, *Arthritis Rheum.*, 25, 591-594, 1982.
46. Fauci, A. S., Mechanisms of the immunosuppressive and anti-inflammatory effects of glucocorticoids, *J. Immunopharmacol.*, 1, 1-25, 1978.
47. Gisler, R. and Schenkel-Hulliger, L., Hormonal regulation the immune response. II. Influence of pituitary and adrenal activity on immune responsiveness in vitro, *Cell Immunol.*, 2, 646-657, 1971.
48. McCrudden, A. B. and Stimson, W. H., Sex hormones and immune function, in *Psychoneuroimmunology*, 2nd ed., Ader, R., Felten, D. L., and Cohen, N., Eds., Academic Press, San Diego, CA, 1991, 475-477.
49. Munck, A. and Guyre, P. M., Glucocorticoids and immune function, in *Psychoneuroimmunology*, 2nd ed., Ader, R., Felten, D. L., and Cohen, N., Eds., Academic Press, San Diego, CA, 1991, 447-460.
50. Nagy, E., Berczi, I., and Friesen, H. G., Regulation of immunity in rats by lactogenic and growth hormones, *Acta Endocrinol.*, 102, 351-357, 1983.
51. Ikeda, T. and Sirbasku, D. A., Purification and properties of a mammary-uterine pituitary tumor cell growth factor from pregnant sheep uterus, *Biol. Chem.*, 259, 4049-4064, 1984.
52. Kappas, A., Jones, H. E. H., and Roitt, I. M., Effects of steroid sex hormones on immunological phenomena, *Nature*, 198, 902, 1963.
53. Van Vollenhorn, R. F. and McGuire, J. L., Estrogen, progesterone and testosterone: can they be used to treat autoimmune disease?, *Cleveland Clin. J. Med.*, 61, 276-284, 1994.
54. Brown, G., Seggle, J., and Ettigi, P., Stress, hormone responses, and cancer, in *Cancer, Stress, and Death*, Tache, J., Selye, H., and Day, S. B., Eds., Plenum, New York, 1979, 29-39.
55. Lippman, M. E., Yarbro, G. K., and Leventhal, B. G., Effects of glucocorticoids on F_c receptors of a human granulocyte cell line, *Cancer Research*, 38, 4251-4256, 1978.
56. Levy, S., Herberman, R., Maluish, A. et al., Prognostic risk assessment in primary breast cancer by behavioral and immunological parameters, *Health Psychol.*, 4, 99-113, 1985.
57. Levy, S., Herberman, R., Lippman, M. et al., Correlation of stress factors with sustained depression of natural killer cell activity and predicted prognosis in patients with breast cancer, *J. Clin. Oncol.*, 5, 348-353, 1987.
58. Bovbjerg, D. H. and Valdimarsdottir, H., Familial cancer, emotional distress, and low natural cytotoxic activity in healthy women, *Res. Nurse Health*, 16, 395-404, 1993.
59. Shamberger, R. J., Tytko, S. A., and Willis, C. E., Antioxidants in cereals and in food preservatives and declining cancer mortality, *Cleveland Clin. O.*, 39, 119-124, 1972.

60. Horrobin, D. F., Manku, M. S., Oka, M., Morgan, R. O., Cunnane, S. C., Ally, A. I., Ghayur, T., Schweitzer, M., and Karmali, R. A., The nutritional regulation of T lymphocyte function, *Med. Hypotheses*, 5, 969-985, 1979.
61. Wynder, E. L., Dietary habits and cancer epidemiology, *Cancer*, 43, 1955-1961, 1979.
62. Nördenstrom, B. E. W., *Biologically Closed Electric Circuits: Clinical Experimental and Theoretical Evidence for an Additional Circulatory System*, Nordic Medical Publications, Stockholm, 1983, 358.
63. Azavedo, E., Svane, G., and Nördenstrom, B., Radiological evidence of response to electrochemical treatment of breast cancer, *Clin. Radiol.*, 43, 84-87, 1991.
64. Nördenstrom, B. E., Impact of biologically closed electric circuits (BCEC) on structure and function, *Integr. Physiol. Behav. Sci.*, 27, 285-303, 1992.
65. Belehraddek, M., Domenge, C., Luboinski, B., Orlowski, S., Belehraddek, J., and Mir, L. M., Electrotherapy, a new antitumor treatment. First clinical phase I-II trial, *Cancer*, 72, 3694-3700, 1993.
66. Belehraddek, J., Orlowski, S., Poddevin, B., Paoletti, C., and Mir, L. M., Electrotherapy of spontaneous mammary tumours in mice, *Eur. J. Cancer*, 27, 73-76, 1991.
67. Salford, L. G., Persson, B. R., Brun, A., Ceberg, C. P., Kongstad, P. C., and Mir, L. M., A new brain tumor therapy combining bleomycin with in vivo electroporation, *Biochem. Biophys. Res. Commun.*, 194, 938-943, 1993.
68. Rosch, P. J., Future directions in psychoneuroimmunology: psychoneuroimmunology?, in *Stress, the Immune System and Psychiatry*, Leonard, B. and Miller, K., Eds., John Wiley & Sons, Chichester, 1995.
69. Sanyal, P. K., *History of Medicine and Pharmacy in India*, Amitava Sanyal, Calcutta, 1964.
70. Cramer, D. L., The semantics of cancer, *Int. Med.*, 2, 9, 1981.
71. Gendron, D., *Enquiries Into The Nature, Knowledge And Cure Of Cancer*, London, 1701.
72. Burrows, J., *A New Practical Essay on Cancer*, London, 1783.
73. Nunn, T. W., *On Cancer of the Breast*, J & A Churchill, London, 1882, 123.
74. Stern, R., as quoted in Suess, R., Kinzel, V., and Scribner, J. P., *Cancer—Experiments and Concepts*, Springer-Verlag, New York, 1973.
75. Walshe, W. H., *The Nature and Treatment of Cancer*, Taylor & Walton, London, 1846.
76. Snow, H., *Cancer and the Cancer Process*, Churchill, London, 1893.
77. Kowal, S. J., Emotions as a cause of cancer: eighteenth and nineteenth century contributions, *Psychoanal. Rev.*, 42, 217-227, 1955.
78. Guy, R., *An Essay On Schirrhous Tumours And Cancer*, W. Owen, London, 1759.
79. Gibson, W. T., *The Etiology and Nature of Cancerous and Other Growths*, John Bale Sons & Danielsson, London, 1909.
80. Evans, E., *A Psychological Study Of Cancer*, Dodd-Mead and Co., New York, 1926.
81. Kissen, D. M., Personality characteristics in males conducive to lung cancer, *Br. J. Med. Psychol.*, 36, 27-36, 1963.
82. Kissen, D. M., Psychosocial factors, personality and lung cancer, *Br. J. Med. Psychol.*, 40, 29-43, 1967.

83. Kissen, D. M., Brown, R. I. F., and Kissen, M. A., A further report on personality and psychosocial factors in lung cancer, *Ann. NY Acad. Sci.*, 164, 535-545, 1969.
84. Kissen, D., Psychosocial factors, personality and lung cancer in men aged 55-64, *Br. J. Med. Psychol.*, 40, 29-43, 1967.
85. Kissen, D., The present status of psychosomatic cancer research, *Geriatrics*, 24, 129, 1969.
86. Schmale, A. H. and Iker, H. P., The affect of hopelessness and the development of cancer. I. The prediction of uterine cervical cancer in women with atypical cytology, *Psychosom. Med.*, 28, 714-721, 1966.
87. Schmale, A. H. and Iker, H. P., The affect of hopelessness and the development of cancer, *Psychosom. Med.*, 28, 714-721, 1966.
88. Schmale, A. H. and Iker, H. P., The psychological setting of uterine cervical Cancer, *Ann. NY Acad. Sci.*, 25, 807-813, 1966.
89. Schmale, A. H. and Iker, H., Hopelessness as a predictor of cervical cancer, *Soc. Sci. Med.*, 5, 95-100, 1971.
90. Lambley, P., The role of psychological processes in the aetiology and treatment of cervical cancer: a biopsychological perspective, *Br. J. Med. Psychol.*, 66, 43-60, 1993.
91. Greene, W. A. and Miller, G., Psychological factors and reticuloendothelial disease, *Psychosom. Med.*, 20, 124-144, 1958.
92. Greene, W. A., The psychosocial setting of the development of leukemia and lymphoma, *Ann. NY Acad. Sci.*, 125, 794-801, 1966
93. Thomas, C. B. and Duszynski, K. R., Closeness to parents and the family constellation in a prospective study of five disease states: suicide, mental illness, malignant tumour, hypertension and coronary heart disease, *Johns Hopkins Med. J.*, 134, 251-270, 1974.
94. Thomas, C. B., Duszynski, K. R., and Shaffer, J. W., Family attitudes reported in youth as potential predictors of cancer, *Psychosom. Med.*, 41, 287-302, 1979.
95. LeShan, L. and Worthington, R. E., Some recurrent life history patterns observed in patients with malignant disease, *J. Nerv. Ment. Dis.*, 124, 460-465, 1956.
96. LeShan, L. L., An emotional life-history pattern associated with neoplastic disease, *Ann. NY Acad. Sci.*, 164, 546-557, 1969.
97. LeShan, L., Psychological states as factors in the development of malignant disease: a critical review, *J. Natl. Cancer Inst.*, 22, 1-18, 1959.
98. Le Shan, L., *You Can Fight For Your Life*, M. Evans, New York, 1977.
99. Tolstoy, L., *The Death of Ivan Ilyitch*, Solotaroff, L., Ed., Bantam, New York, 1981.
100. Auden, W. H., *Collected Poems*, Random House, New York, 1991.
101. Sontag, S., *Illness as Metaphor*, Farrar, Straus, and Giroux, New York, 1977.
102. Rosch, P. J., Some thoughts on the epidemiology of cancer, in *Readings in Oncology*, Day, S. B., Sugarbaker, E. V., and Rosch, P. J., Eds. The International Foundation for Biosocial Development and Human Health, New York, 1980, 1-6.
103. Rosch, P. J., Stress and cancer, in *Psychosocial Stress and Cancer*, Cooper, C. L., Ed., John Wiley & Sons, London, 1984, 3-19.
104. Riley, V., Mouse mammary tumors: alteration of incidence as apparent function of stress, *Science*, 189, 465-467, 1975.

105. Riley, V., Cancer and stress: overview and critique, *Cancer Detection Prevention*, 2, 163-195, 1979.
106. Riley, V., Psychoneuroendocrine influences on immunocompetence and neoplasia, *Science*, 212, 1100-1109, 1981.
107. Kissen, D., Psychosocial factors, personality and lung cancer in men aged 55-64, *Br. J. Med. Psychol.*, 40, 29-43, 1967.
108. Visintainer, M. A., Volpicelli, J. R., and Seligman, M. E. P., Tumor rejection in rats after inescapable or escapable shock, *Science*, 216, 437-439, 1982.
109. Lemonde, P., Influence of fighting on leukemia in mice, *Proc. Soc. Exp. Biol. Med.*, 102, 292-295, 1959.
110. Greer, S. and Morris, T., Psychological attributes of women who develop breast cancer: a controlled study, *J. Psychosom. Res.*, 19, 147, 1975.
111. Greer, S., Morris, T., and Pettingale, K. W., Psychological response to breast cancer: effect on outcome, *Lancet*, 2, 785-787, 1979.
112. Greer, S., Morris, T., Pettingale, K., and Haybittle, J., Mental attitudes to cancer: an additional prognostic factor, *Lancet*, 1, 750, 1985.
113. Greer, S., Moorey, S., Baruch, J. D. R., Watson, M. et al., Adjuvant psychological therapy for patients with cancer: a prospective randomized trial, *Br. Med. J.*, 304, 675-680, 1992.
114. Holden, C., Cancer and the mind: how are they connected?, *Science*, 200, 1363-1368, 1978.
115. Peters, L. J. and Mason, K. A., Influence of stress on experimental cancer, in *Mind and Cancer Prognosis*, Stoll, B. A., Ed., John Wiley & Sons, New York, 1979, 104-124.
116. Cassileth, B. R., Lusk, E. J., Miller, D. S. et al., Psychological correlates of survival in advanced malignant disease?, *N. Engl. J. Med.*, 312, 1551-1555, 1985.
117. Jamison, R. N., Burish, T. G., and Wallston, K. A., Psychogenic factors in predicting survival of breast cancer patients, *J. Clin. Oncol.*, 5, 772-798, 1987.
118. Levenson, J. L. and Bernis, C., The role of psychological factors in cancer onset and progression, *Psychosomatics*, 32, 124-132, 1991.
119. Fox, B. H., Premorbid psychological factors as related to cancer incidence, *J. Behav. Med.*, 1, 45-133, 1978.
120. Fox, B. H. and Newberry, B. H., *Impact of Psychoendocrine Systems in Cancer and Immunology*, C. J. Hogrefe, Lewiston, NY, 1984.
121. Riley, V., Introduction: stress-cancer contradictions—a continuing puzzle-ment, *Cancer Detect. Prev.*, 2, 159-162, 1979.
122. Greer, S. and Morris, T., The study of psychological factors in breast cancer: problems of method, *Soc. Sci. Med.*, 12, 129-134, 1978.
123. Miller, T. and Spratt, J. S., Critical review of reported psychological correlates of cancer prognosis and growth, in *Mind and Cancer Prognosis*, Stoll, B. A., Ed., John Wiley & Sons, New York, 1979, 31-37.
124. Bieliauskas, L. A. and Garron, D. C., Psychological depression and cancer, *Gen. Hosp. Psychiatry*, 4, 187-195, 1982.
125. Shekelle, R. B., Raynor, W. J., Ostfeld, A. M., Garron, D. C., Bieliauskas, L. A., Liu, S. C., Maliza, C., and Paul, O., Psychological depression and 17-year risk of death from cancer, *Psychosom. Med.*, 43, 117-125, 1981.
126. Nerozzi, D., Santoni, A., Bersani, G. et al., Reduced natural killer cell activity in major depression: neuroendocrine implications, *Psychoneuroendocrinology*, 14, 295-301, 1989.

127. Irwin, M., Patterson, T., Smith, T. L. et al., Reduction of immune function in life stress and depression, *Biol. Psychiatry*, 27, 22-30, 1990.
128. Linn, B. S., Linn, M. W., and Jensen, J., Degree of depression and immune responsiveness, *Psychosom. Med.*, 44, 128-129, 1982.
129. Gossarth-Maticek, R., Bastiaans, J., and Kanazin, D. T., Psychosocial factors as strong predictors of mortality from cancer, ischemic heart disease and stroke: the Yugoslav prospective study, *J. Psychosom. Res.*, 29, 167-176, 1985.
130. Gossarth-Maticek, R., Psychosocial predictors of cancer and internal diseases: an overview, *Psychother. Psychosom.*, 33, 122-128, 1980.
131. Greer, S. and Watson, M., Towards a psychobiological model of cancer: psychological considerations, *Soc. Sci. Med.*, 20, 773-777, 1985.
132. Morris, T., Greer, S., Pettingale, K. W., and Watson, M., Patterns of expression of anger and their psychological correlates in women with breast cancer, *J. Psychosom. Res.*, 25, 111-117, 1981.
133. Pettingale, K. W., Greer, S., and Tee, D. E. H., Serum IGA and emotional expression in breast cancer patients, *J. Psychosom. Res.*, 21, 395-399, 1977.
134. Traue, H. C. and Pennebaker, J. W., *Emotion Inhibition and Health*, Hogrefe & Huber Publishers, Kirkland, WA, 1993.
135. Balitsky, K. P., Shmalko, Y. P., and Pinchuk, V. G., Stress, cancer: stress modulation of the metastatic process, in *Cancer, Stress, and Death*, 2nd ed., Day, S. B., Ed., Plenum Publishing, New York, 1986, 113-129.
136. Bammer, K., Stress, spread and cancer, in *Stress and Cancer*, Bammer, K. and Newberry, B. H., Eds., C. J. Hogrefe, Toronto, 1981, 137-163.
137. Spiegel, D. and Sands, S. H., Psychological influences on metastatic disease progression, in *Progressive States of Malignant Neoplastic Growth*, Kaiser, H. E., Ed., Martinus Nijhoff, Dordrecht, The Netherlands, 1985, 74-89.
138. Derogatis, L. R., Abeloff, M. D., and Melisaratos, N., Psychological coping mechanisms and survival time in metastatic breast cancer, *JAMA*, 242, 1504-1508, 1979.
139. Lehrer, S., Life change and lung cancer, *J. Hum. Stress*, 7, 7-11, 1981.
140. Lehrer, S., Life change and gastric cancer, *Psychosom. Med.*, 42, 499-502, 1980.
141. Stephenson, J. H. and Grace, W. J., Life stress and cancer of the cervix, *Psychosom. Med.*, 16, 287-294, 1954.
142. Helsing, K. J. and Szklo, M., Mortality after bereavement, *Am. J. Epidemiol.*, 114, 41-52, 1981.
143. Stroebe, W. and Stroebe, M. S., *Bereavement and Health*, Cambridge University Press, Cambridge, 1987.
144. Schneider, J., *Stress, Loss and Grief*, University Park Press, Baltimore, 1984.
145. Bartrop, R. W., Luckhurst, E., Lazarus, L., Kiloh, L. G., and Penny, R., Depressed lymphocyte function after bereavement, *Lancet*, 1, 834-836, 1977.
146. Schleifer, S. J., Keller, S. E., Camerino, M. et al., Suppression of lymphocyte stimulation following bereavement, *JAMA*, 250, 374-377, 1983.
147. Pettingale, K. W. and Hussein, M., Changes in immune status following conjugal bereavement, *Stress Med.*, 10, 145-150, 1994.
148. Pettingale, K. W., Watson, H., Tee, D. E. H., Inayat, Q., and Alhaq, A., A pathological grief, psychiatric symptoms and immune status following conjugal bereavement, *Stress Med.*, 5, 77-83, 1989.

149. Holmes, T. H. and Rahe, R.H., The social readjustment rating scale, *J. Psychosom. Med.*, 11, 213-218, 1967.
150. Kune, S., Kune, G. A., Watson, L. F., and Rahe, R. H., Recent life change and large bowel cancer: data from the Melbourne Colorectal Cancer Study, *J. Clin. Epidemiol.*, 44, 57-68, 1991.
151. Kune, S., Stressful life events and cancer, *Epidemiology*, 4, 395-397, 1993.
152. Irwin, M., Daniels, M., and Weiner, H., Immune and neuroendocrine changes during bereavement, *Psychiatr. Clin. North Am.*, 10, 449-465, 1987.
153. Irwin, M., Daniels, M., Smith, T. L., Bloom, F., and Weiner, H., Impaired natural killer cell activity during bereavement, *Brain Behav. Immun.*, 1, 98-104, 1987.
154. Stein, M., Miller, A. H., and Trestman, R. L., Depression, the immune system, and health and illness, *Arch. Gen. Psychiatry*, 48, 171-177, 1991.
155. Kronfol, Z., Silva, J., Greden, J., Dembinski, S., and Carroll, B. J., Cell-mediated immunity in melancholia, *Psychosom. Med.*, 44, 304, 1982.
156. Marriott, D., Kirkwood, B. J., and Stough, C., Immunological effects of unemployment, *Lancet*, 344, 269-270, 1994.
157. Kegeles, S. S., Relationship of sociocultural factors to cancer, in *Cancer: The Behavioral Dimensions*, Cullen, J. W., Fox, B. H., and Isom, R. N., Eds., Raven Press, New York, 1976, 108-125.
158. Adelstein, A. M., Life-style in occupational cancer, *J. Toxic. Environ. Health*, 6, 953-962, 1980.
159. Jenkins, C. D., Social environment and cancer mortality in men, *N. Engl. J. Med.*, 308, 395-398, 1983.
160. Shaffer, J. W., Graves, P. L., Swank, R. T. et al., Clustering of personality traits in youth and the subsequent development of cancer among physicians, *J. Behav. Med.*, 10, 441-447, 1987.
161. Rosch, P. J., Mind and cancer, *Lancet*, 1, 1302, 1979.
162. Rosch, P. J., Lifestyle and cancer, *NY State Med. J.*, 80, 2031-2038, 1980.
163. Trichopoulos, D., MacMahon, B., and Brown, J., Socioeconomic status, urine estrogens, and breast cancer risk, *J. Natl. Cancer Inst.*, 64, 753-755, 1980.
164. Morrison, F. R., Psychosocial factors in the etiology of cancer, *Diss. Abstr. Int.*, 42, 155B, 1981.
165. Cox, T. and Mackay, C., Psychosocial factors and psychophysiological mechanisms in the aetiology and development of cancers, *Soc. Sci. Med.*, 16, 381-396, 1982.
166. Kiecolt-Glaser, J. K. and Glaser, R., Stress and immune function in humans, in *Psychoneuroimmunology*, 2nd ed., Ader, R., Felten, D. L., and Cohen, N., Eds., Academic Press, San Diego, CA., 1991, 849-867.
167. Warren, S. and Canavan, M. M., Frequency of cancer in the insane, *N. Engl. J. Med.*, 210, 739, 1934.
168. Ananth, J. and Bernstein, M., Cancer less common in psychiatric patients, *Psychosomatics*, 18, 44-46, 1977.
169. Derogatis, L. R., Morrow, G. R., Fetting, J., Penman, D., Piasetsky, S., Schmale, A. M., Henrichs, M., and Carnicke, C. L., Jr., The prevalence of psychiatric disorders among cancer patients, *JAMA*, 249, 751-757, 1983.
170. Levitan, L. J., Levitan, H., and Levitan, M., The incidence of cancer in psychiatric patients: cancer and the emotions: a review, *Mt. Sinai J. Med.*, 47, 627-631, 1980.

171. Kune, G. A., Kune, S., Watson, L. F., and Bahnson, C. B., Personality as a risk factor in large bowel cancer: data from the Melbourne Colorectal Cancer Study, *Psychol. Med.*, 21, 29-41, 1991.
172. Bahnson, C. B., Stress and cancer: the state of the art. I, *Psychosomatics*, 21, 975-981, 1980; Stress and cancer: the state of the art. II; *Psychosomatics*, 22, 207-220, 1981.
173. Brown, F., The relationship between cancer and personality, *Ann. NY Acad. Sci.*, 125, 865-875, 1966.
174. Dattore, P. J., Shontz, F. C., and Coyne, L., Premorbid personality differentiation of cancer and non-cancer groups: a test of the hypothesis of cancer proneness, *J. Consult. Clin. Psychol.*, 48, 388-394, 1980.
175. Dunbar, F., *Emotions and Bodily Changes*, 4th ed., Columbia University Press, New York, 1954.
176. Hagnell, O., The premorbid personality of persons who develop cancer in a total population investigated in 1947 and 1957, *Ann. NY Acad. Sci.*, 125, 846-864, 1966.
177. Kissen, D. M., The significance of personality in lung cancer in men, *Ann. NY Acad. Sci.*, 125, 820-826, 1966.
178. Le Shan, L. L. and Worthington, R. E., Personality as a factor in the pathogenesis of cancer, *Br. J. Mod. Psychol.*, 29, 49-56, 1956.
179. Eysenck, H. J., Personality, stress, and motivational factors in drinking as determinants of risk for cancer and coronary heart disease, *Psychol. Rep.*, 69, 1027-1043, 1991.
180. Eysenck, H. J., Grossarth-Maticek, R., and Everitt, B., Personality, stress, smoking, and genetic predisposition as synergistic risk factors for cancer and coronary heart disease, *Integr. Physiol. Behav. Sci.*, 26, 309-322, 1991.
181. Cooper, C. L. and Faragher, E. B., Psychosocial stress and breast cancer: the inter-relationship between stress events, coping strategies and personality, *Epidemiol. Rev.*, 15, 163-168, 1993.
182. Cooper, C. L., The social-psychological precursors to cancer, *J. Hum. Stress*, 10, 4-11, 1984.
183. Temoshok, L. and Dreher, H., *The Type C Connection: The Behavioral Links to Cancer and Your Health*, Penguin, New York, 1993.
184. Temoshok, L., Heller, B. W., and Sageviel, R. W. et al., The relationship of psychological factors of prognostic indicators in cutaneous malignant melanoma, *J. Psychosom. Res.*, 29, 139-153, 1985.
185. Kneier, A. W. and Temoshok, L., Repressive coping reactions in patients with malignant melanoma as compared to cardiovascular patients, *J. Psychosom. Res.*, 28, 145-155, 1984.
186. Renneker, R., Cancer and psychotherapy, in *Psychotherapeutic Treatment of Cancer Patients*, Goldberg, J., Ed., Free Press, New York, 1981, 131-166.
187. Gibertini, M., Reintgen, D. S., and Baile, W. F., Psychosocial aspects of melanoma, *Ann. Plast. Surg.*, 28, 17-21, 1992.
188. Havlik, R. J., Vukasin, A. P., and Ariyan, S., The impact of stress on the clinical presentation of melanoma, *Plast. Reconstr. Surg.*, 90, 57-61, 1992.
189. Breedis, C., Induction of accessory limbs and of sarcoma in the newt with carcinogenic substances, *Cancer Res.*, 12, 861-866, 1952.

190. Eguchi, E. and Watanabe, K., Elicitation of lens formation from the ventral iris epithelium of the newt by a carcinogen *N*-methyl-*N*-nitro-*N*-nitrosoguanidine, *J. Embryol. Exp. Morphol.*, 30, 63-71, 1973.
191. Seilerrn-Aspeng, F. and Kratochwil, K., Relation between regeneration and tumor growth, in *Regeneration in Animals and Related Problems*, Kioutsis, V. and Transpusch, H., Eds., North Holland, Amsterdam, 1965, 452-473.
192. Donaldson, D. J. and Mason, J. M., Cancer related aspects of regeneration research: a review, *Growth*, 39, 475-496, 1975.
193. Pearson, H. A., Johnston, D., Smith, K. A., and Touloukian, R. J., The born-again spleen. Return of splenic function after splenectomy for trauma, *N. Engl. J. Med.*, 298, 1389-1392, 1978.
194. Selye, H., Foreword, in *Cancer, Stress, and Death*, Taché, J., Selye, H., and Day, S. B., Eds., Plenum Publishing, New York, 1979, xii.
195. LeConté, J., Statistical researches on cancer, *South. Med Surg. J.*, 4, 273-274, 1846.
196. Bainbridge, W. S., *The Cancer Problem*, Macmillan, New York, 1914.
197. Hoffman, F. L., *Mortality From Cancer Throughout The World*, Prudential Press, Newark, 1916.
198. Schweitzer, A., *Forest Hospital of Lamborene*, Holt, Oxford, 1931.
199. Stefansson, V., *Cancer: Disease of Civilization?*, Hill and Wang, New York 1960.
200. Hay, W. H., Cancer: A disease of either election or ignorance, *Am. J. Cancer*, 6, 410-422, 1927.
201. Roberts, M., *Malignancy and Evolution*, Grayson, New York, 1934.
202. Moore, C. H., *The Antecedents of Cancer*, London, Longmans, 1865.
203. Powell, C., *The Pathology of Cancer*, Macmillan, New York, 1908.
204. Berglas, A., *Cancer: Its Nature, Cause and Cure*, Pasteur Institute Paris, 1957.
205. Donnison, C. P., *Civilization and Disease*, William Wood, Baltimore, 1938.
206. Halliday, J. L., *Psychosocial Medicine: A Study of the Sick Society*, W. W. Norton, New York, 1948.
207. Dubos, R., Biological and social aspects of tuberculosis, *Bull. NY Acad. Med.*, 27, 351, 1951.
208. Cassell, J., The contribution of the social environment to host resistance, *Am. J. Epidemiol.*, 104, 7-13, 1976.
209. Antonovsky, A., *Health, Stress, and Coping: New Perspectives on Mental and Physical Well-Being*, Jossey-Bass, San Francisco, 1979.
210. Wolf, S., Herrenkohl, R. C., Lasker, J., Egloff, J., Philips, B. U., and Bruhn, J. G., Roseto, Pennsylvania, 25 years later—highlights of a medical and sociological survey, *Trans. Am. Clin. Climatol. Soc.*, 100, 57-67, 1988.
211. Bruhn, J. and Wolf, S., *The Roseto Story: An Anatomy of Health*, University of Oklahoma Press, Norman, 1978.
212. Miller, J., *Living Systems*, McGraw-Hill, New York, 1978.
213. Yamasaki, H., Aberrant expression and function of gap junctions during carcinogenesis, in *Nongenotoxic Mechanisms in Carcinogenesis*, Butterworth, B. E. and Slaga, T. J., Eds., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1987, 297-316.
214. Rosch, P. J., Stress and electromedicine, *Med. Electron.*, 19(4), 124-128, 1989.

215. Tromp, S. W., Meteorological stress and cancer, in *Stress and Cancer*, Bammer, K. and Newberry, B. H., Eds., C. J. Hogrefe, Toronto, 1981, 164-185.
216. Pribram, K., *Rethinking Neural Networks: Quantum Fields and Biological Data*, L. Erlbaum, New York, 1993.
217. Bohm, D., *Wholeness and the Implicate Order*, Routledge and Kegan Paul, London, 1980.
218. Shelldrake, R., *Rebirth of Nature*, Bantam, New York, 1992.
219. Kobasa, S., Maddi, S., and Kahn, S., Hardiness and health: a prospective study, *J. Personality Soc. Psychol.*, 42, 168-177, 1982.
220. Achterberg, J., Matthews, S., and Simonton, O. C., Psychology of the exceptional cancer patient—a description of patients who outlive predicted life expectancies, *Psychother. Theory Res. Practice*, 9, 1-21, 1976.
221. Kune, G. A., Kune, S., and Watson, L. F., Perceived religiousness is protective for colorectal cancer: data from the Melbourne Colorectal Cancer Study, *J. R. Soc. Med.*, 86, 645-647, 1993.
222. Ikemi, Y., Akagawa, S., Nakagawa, T., and Sugita, M., Psychosomatic considerations on cancer patients who have made a narrow escape from death, *Dynam. Psychiatry*, 31, 77-92, 1975.
223. Cole, W. H., Spontaneous regression of cancer. The metabolic triumph of the host?, *Ann. NY Acad. Sci.*, 230, 111, 1974.
224. Meares, A., A form of intensive meditation associated with the regression of cancer, *Am. J. Clin. Hypn.*, 25, 114-121, 1982.
225. Meares, A., Regression of osteogenic sarcoma metastases associated with intensive meditation, *Med. J. Aust.*, 2, 433, 1978.
226. Meares, A., Remission of massive metastasis from undifferentiated carcinoma of the lung associated with intensive meditation, *J. Am. Soc. Psychosom. Dent. Med.*, 27, 40-41, 1980.
227. Meares, A., Regression of recurrence of carcinoma of the breast at mastectomy site associated with intensive meditation, *Aust. Fam. Physician*, 10, 218-219, 1981.
228. Meares, A., Regression of cancer after intensive meditation, *Med. J. Aust.*, 2, 184, 1976.
229. Meares, A., The quality of meditation effective in the regression of cancer, *J. Am. Soc. Psychosom. Dent. Med.*, 25, 129-132, 1978.
230. Meares, A., Vivid visualization and dim visual awareness in the regression of cancer in meditation, *J. Am. Soc. Psychosom. Dent. Med.*, 25, 85-88, 1978.
231. Bolen, J. S., Meditation and psychotherapy in the treatment of cancer, *Psychic*, 4, 19-22, 1973.
232. Achterberg, J. and Lawlis, G. F., *Imagery of Cancer*, Institute for Personality and Ability Testing, Champaign, IL, 1978.
233. Clawson, T. A. and Swade, R., The hypnotic control of blood flow and pain: the cure of warts and the potential for the use of hypnosis in the treatment of cancer, *Am. J. Clin. Hypn.*, 17, 160-169, 1975.
234. Hall, H. R., Hypnosis and the immune system: a review with implications for cancer and the psychology of healing, *Am. J. Clin. Hypn.*, 25, 92-103, 1982.
235. Hedge, A. R., Hypnosis in cancer, *Br. J. Med. Hypn.*, 12, 2-5, 1960.
236. Funch, D. P. and Marshall, J., The role of stress, social support and age in survival from breast cancer, *J. Psychosom. Res.*, 27, 177-183, 1983.

237. Funch, D. P. and Mettlin, C., The role of support in relation to recovery from breast surgery, *Soc. Sci. Med.*, 16, 91-98, 1982.
238. Eli, K., Nishimoto, R., Mediansky, L., Mantell, J., and Hamovitch, M., Social relations, social support and survival among patients with cancer, *J. Psychosom. Res.*, 36, 531-541, 1992.
239. Bagenal, F. S., Easton, D. F., Harris, E., Chilvers, C. E. D., and McElwain, T. J., Survival of patients with breast cancer attending Bristol cancer help centre, *Lancet*, 336, 606-610, 1990.
240. Spiegel, D., Bloom, J. R., and Yalom, I. D., Group support for patients with metastatic cancer: a randomized prospective outcome study, *Arch. Gen. Psychiatry*, 38, 527-533, 1981.
241. Spiegel, D., Bloom, J. R., Kraemer, H. C., and Gotthel, E., Effects of psychosocial treatment on survival of patients with metastatic breast cancer, *Lancet*, 2, 888-891, 1989.
242. Ogilvie, H., The human heritage, *Lancet*, ii, 42, 1957.
243. Gordon-Taylor, G., The incomputable factors in cancer prognosis, *Br. Med. J.*, 1, 455, 1959.
244. Pendergrass, E. P., Host resistance and other intangibles in the treatment of cancer, *Am. J. Roentgenol. Radium Ther.*, 85, 891, 1961.
245. Miller, T. R., Psychophysiological aspects of cancer, *Cancer*, 39, 413, 1977.
246. Levy, S. M., Herberman, R. B., Whiteside, T. et al., Perceived social support and tumor estrogen/progesterone receptor status as predictors of natural killer cell activity in breast cancer patients, *Psychosom. Med.*, 52, 73-85, 1990.
247. Rosch, P. J., Stress: cause or cure of cancer, in *Psychotherapeutic Treatment of Cancer Patients*, Goldberg, J., Ed., Free Press, New York, 1981, 39-57.
248. Rosch, P. J., Some thoughts on the epidemiology of cancer, *Cancer, Stress, and Death*, 2nd ed., Day, S. B., Ed., Plenum Publishing, New York, 1986, 293-300.
249. Cannon, W. B., *The Wisdom of the Body*, W. W. Norton, New York, 1932.
250. Bernard, C., *Introduction to the Study of Experimental Medicine*, Flammarion, Paris, 1945 (Original edition 1865).
251. Pasteur, L., quoted in Selye, H., *The Stress of Life*, p. 205, McGraw-Hill, New York, 1956.
252. Osler, W., quoted in Lewison, E. F., Spontaneous regression of breast cancer, *Natl. Cancer Inst. Monogr.*, 44, 23, 1976.
253. Osler, W., *Aequanimitas*, p. 258, McGraw-Hill, New York, 1906.
254. Parry, C. H., quoted in Margetts, E. L., Historical notes on psychosomatic medicine, in *Recent Developments in Psychosomatic Medicine*, Vol. 1, Wittkower, E. D. and Cleghorn, R. A., Eds., Pitman and Sons, London, 1954, 56.