Stress and Cancer: A Disease of Adaptation?

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What happens in the mind of man is always reflected in the diseases of his body.
—René Dubos

The concept that cancer might in some way be related to stress or other emotional factors is probably as old as the history of recorded medicine itself. Galen's treatise on tumors *De Tumoribus* notes that melancholy women (women supposedly having too much black bile—Greek *melas chole*) were much more susceptible to cancer than other females. We find a similar theme resurfacing repeatedly in medical literature, particularly in the last three centuries.

In 1701, the English physician Gendron commented on the effect of "disasters of life as occasion much trouble and grief" in the causation of cancer, and 80 years later Burrows attributed the disease to "the uneasy passions of the mind with which the patient is strongly affected for a long time." Other authors, such as Nunn in 1822, emphasized that emotional factors influenced the growth of tumors of the breast, and Stern noted that cancer of the cervix in

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married women was more common in sensitive and frustrated individuals. 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 the disease." Toward the end of the century, another English physician, Snow, reviewed 250 patients at the London Cancer Hospital and concluded that "the loss of a near relative was an important factor in the development of cancer of the breast and uterus."

I attach particular importance to these observations because the practice of medicine in the 18th and 19th centuries was quite likely more personalized than it is today. Physicians had to rely more upon their own understanding of the significance of the history, emotional setting, and the life style of the patient, rather than on more objective, less personalized criteria such as laboratory studies and technical procedures which characterize today's diagnostic work-up. In addition, the background and training of the physician was more apt to be heavily weighted in literature, the humanities, and philosophy, and it is quite likely that he knew the patient better and longer, knew the family, knew the nature and significance of environmental and personal background events, and had more time to spend with the patient. Thus, by virtue of his own education and orientation and personalized approach, the doctor of that time might well exhibit a greater sensitivity and awareness to this subtle relationship than is now possible in the frenetic pace of today's often superspecialized medical practice.

Lest this be misinterpreted as a denigration of the modern physician, it should be noted that in the present century, individuals from a wide spectrum of medical disciplines, utilizing a variety of more sophisticated and objective techniques, have been able to corroborate and amplify the thesis that emotional factors have an important etiologic role in the development of malignancy. Evans, a Jungian psychoanalyst, pointed out that many cancer patients lost a close emotional relation before the onset of their illness, and in the last 20 years, there has been a flurry of interest in this subject from a number of other disciplines. Using psychological tests, the distinguished British chest physician David Kissen first called attention to the fact that there were certain predominant personality

traits in patients with cancer of the lung, which he characterized as being associated with an inhibition to express actual emotions. Schmale and Iker, in the United States, were able to predict cancer of the cervix with almost 75% accuracy in women who were entirely asymptomatic but who had suspicious Pap smears merely by evaluating a personality questionnaire. They concluded that this disorder occurred most often in individuals with a "helplessness-prone personality" or with a sense of hopeless frustration due to an irresolvable conflict during the preceding six months. In studies of life histories of three sets of identical twins, Greene, a hematologist at the University of Rochester, found that the twin out of each set who contracted and died of leukemia had experienced a psychological upheaval, in contradistinction to the healthy twin, who had not undergone any emotional trauma. In a 15-year study of patients with lymphoma or leukemia, Greene found that the diseases were apt to occur in a setting of emotional loss or separation which engendered feelings of anxiety, anger, sadness, or hopelessness.

Lawrence LeShan, a New York psychoanalyst, has been preoccupied with this subject for the past 20 years. Utilizing Rorschach techniques (inkblot tests), Thematic Apperception Tests, the Worthington Personal History, structured personal interviews, and interviews with close relatives of the patients, he has concluded that the most significant link in the development of a malignancy is the loss of the patient's *raison d'être* (hopelessness/helplessness)—inability on the part of the individual to express anger or resentment, a marked amount of self-dislike and distrust, and most significantly, for our purposes, loss of an important emotional relationship.

About 30 years ago, Dr. Caroline Bedell Thomas, Professor of Medicine at Johns Hopkins Hospital, commenced a psychosocial study of medical students, since they could be closely observed during their four years at medical school and, as intelligent physicians, could be relied upon to cooperate in follow-up studies for the remainder of their lives. She was initially concerned with determining what factors might be of value in predicting and preventing hypertension and coronary artery disease, and she accumulated detailed data consisting of demographic and familial factors, genetic, physiologic, psychologic, and metabolic characteristics.

Thomas was able to do this by utilizing several psychologic stress tests, a Habits of Nervous Tension Questionnaire, a Family Attitude Questionnaire, and two projective psychological tests, the Rorschach and the Figure Drawing Tests. The studies soon expanded into other areas by virtue of unexpected information which indicated possible predictable precursors for mental illness, emotional disturbance, suicide, and cancer. Dr. Thomas's data suggest that cancer tends to occur in individuals who are low-key, nonaggressive, and who do not express their emotions. Many of the individuals tended to be rather lonely persons without any close parental affiliation, or who had figuratively "lost their parent."

Novelists and poets might be expected, by virtue of their sensitivity, to appreciate such relationships. Indeed, Tolstoy's *The Death of Ivan Iliyich* bears such a theme. It was reiterated by the American poet W. H. Auden in "Miss Gee":*

Doctor Thomas sat over his dinner
Though his wife was waiting to ring,
Rolling his bread into pellets,
Said, "Cancer's a funny thing.

Nobody knows what the cause is,
Though some pretend they do;
It's like some hidden assassin
Waiting to strike at you.

Childless women get it,
And men when they retire;
It's as if there had to be some outlet
For their foiled creative fire."
. . . . . .

Emotional loss and frustration of ambitions due to political defeat were viewed by several commentators as playing an important role in the cancers of Napoleon, Ulysses S. Grant, Robert Taft, and Hubert Humphrey.

Apart from its possible causative role in the development of cancer, stress has also been implicated in determining the rate of

*From *Collected Poems* by W. H. Auden, edited by Edward Mendelson, copyright 1940 and renewed 1968 by W. H. Auden. Reprinted by permission of Random House, Inc.

spread and the ultimate course of an established malignancy. All physicians have had the experience of seeing a malignant tumor spread like wildfire despite all therapeutic efforts, whereas in another patient of the same age and sex, an apparently identical malignancy behaves in a rather indolent fashion, with or without treatment. Many authors have alleged that the rate of tumor growth can be predicted based upon certain personality traits similar to those described above. One frequently quoted study done about 25 years ago by Blumberg examined two groups of cancer patients matched for age, intelligence, and the state of their cancers; all the patients knew their diagnosis. The patients were studied following their initial treatment when they were, relatively speaking, "feeling well." Those patients dying in less than two years were compared with those living for more than six years and were found to have significantly poorer outlets for emotional discharge. About ten years ago, Stavraky conducted a similar study on 204 cancer patients and concluded that the group with the most favorable outlook consisted of those who were able to show strong feelings under severe stress without loss of emotional control. Again, we encounter the feeling that "giving up" or loss of *"raison d'être"* may be an important factor in whether the patient survives and in determining the course of the disease. Although many of these studies would not satisfy scientific statistical criteria, they are provocative.

Nicholas Rogentine, an immunologist at the National Cancer Institute, recently reported on a group of patients who had apparently been operated on successfully for malignant melanoma, a particularly lethal form of skin cancer. He found that relapse did not occur among patients who maximized the significance of their illness, again supporting the theory that repression and denial are related to a more discouraging prognosis. His findings reinforce the value of work by LeShan, the Simontons, and others in encouraging the patient's active emotional participation as part of the management of his illness.

There are certain difficulties inherent in any attempt to prove a relationship between stress and cancer. First of all, the terms themselves are difficult to define and quantify. We all know or sense what stress is, but it is very difficult to get any unanimity of opinion on a precise definition. It is obvious that what may be damag-

ingly stressful for one person is decidedly not for another individual. One man's meat in this instance might well be another man's poison, or more elegantly, one man's stress is another's *métier*.

It is equally difficult to equate or quantify different types of cancers. When does the malignant process start? How can its growth be accurately measured? Can malignancies such as skin cancer, tumors of the lung, colon, breast, and brain, and leukemia all be lumped together for purposes of a discussion such as ours? Similarly, what is the effect on the patient—after he has been told that he has a malignancy—in terms of altering his own personality and inducing further harmful stress? As we shall see later, it is quite likely that the *manner* in which the diagnosis and prognosis are presented may definitely influence the subsequent course of the tumor. These are only some of the variables that make it difficult to construct an experimental model that would be scientifically acceptable, but such difficulties do not preclude presenting persuasive evidence from which rational deductions may be drawn.

A masterful analysis of the multiple problems, and some possible approaches to the problem may be found in Fox's recent comprehensive analysis of the subject. One of the most intriguing and convincing clinical approaches to an understanding of the relationship between stress and illness in general is to be found in the work of Thomas Holmes, Professor of Psychiatry at the University of Washington, and his group, who identified 43 life change events and rated them according to magnitude, the criterion being how much the individual had to cope with or alter his life style as a result of the event. The following is an abridged version of how they quantified stress:

Event	Score
Death of a spouse	100
Divorce	73
Marital separation	65
Death of a close family member	63
Jail term	63
Marriage	50
Fired from job	47
Retirement	45

Event	Score
Sex difficulties	39
Death of a close friend	37
Change in number of arguments with spouse	35
Son or daughter leaves home	29
Trouble with in-laws	29
Outstanding personal achievement	28
Change in eating habits	15
Vacation	13
Traffic ticket	11

By means of a questionnaire which measures the number and types of life change events in the preceding six-month, one-year, or two-year period, it is possible to predict with some accuracy whether an individual will become ill within the next six months and, furthermore, to some extent, how serious that illness will be. The most serious type of illness is cancer. Looking at the chart, one notes that death of a spouse is considered to be the most significant life change event. The next highest event, which is more than a quarter of the way down the scale, is divorce, followed by marital separation and death of a close family member. (The first five items have been copied directly.) It is significant that those events of the greatest magnitude represent loss of a close personal relationship and far outweigh the succeeding items.

Holmes's research, indicating that death of a spouse or divorce represent the most damaging types of stress, is supported by two statistical studies dealing with cancer in females as shown in Tables 1 and 2. Table I shows the relationship of marital status in females in the United States to mortality from cancer of the breast, female genital organs, and other sites. Table 2 presents age-mated statistics from Great Britain which show similar findings demonstrating the validity of the non-age-mated figures in Table 1—although, again, statisticians might require more data to justify this conclusion.

The effects of stress on cancer in laboratory animals provides another source of relevant data. Workers in the school of the great Russian psychologist and physiologist Pavlov (famous for his description of the "conditioned reflex") reported that dogs subjected to severe and chronic stress had a marked increase in malignancy

TABLE 1. Cancer Mortality Rates per 100,000 Living Population of the United States 1929-1931

Marital Status	Breast	Uterus	Ovary-fallopian tubes	Vulva and vagina	All other sites	Total
Single	15.0	9.0	3.3	.5	3.4	61.2
Married	24.5	35.0	4.7	.8	11.8	137.7
Divorced	29.3	57.2	6.0	1.5	81.8	175.8
Widowed	74.4	94.4	0.6	4.3	344.4	527.1

of the internal organs. Many other studies have been done in laboratory animals relating to the effects of stress on the transmission of experimental cancer and the course of cancer in laboratory animals. Dr. Vernon Riley and his group at the Pacific Northwest Research Foundation in Seattle selected a strain of mice that is highly cancer-prone, and under usual laboratory conditions, 60% of the animals developed tumors within 8-18 months after birth. When the research team put the mice behind a protective barrier insulating them from the normal laboratory commotion and noise—which conceivably could generate anxiety and stress—only 7% of the mice developed cancer during a 14-month period. Conversely, a separate experiment showed that simply rotating the animals gently on a turntable was sufficient to promote significantly higher cancer rates. Another study done at Stanford University School of Medicine dealt with the effects of stress on virus-induced tumors in mice. The maximum tumor size was increased by three days of electric shock stress following the virus inoculation, and it was also noted that female mice spontaneously displaying fighting or antagonistic behavior developed smaller tumors. However, there may also be certain adaptive responses to stress which are helpful,

TABLE 2. Death Rates per 100,000 Living, All Forms of Cancer, England and Wales, 1930-1932

Marital Status	Age 25	Age 35	Age 45	Age 55	Age 65	Age 70 and over
Spinsters	126 ± 0.6	68 ± 2.0	219 ± 4.1	416 ± 6.7	635 ± 13.1	961 ± 14.5
Married	169 ± 0.5	75.1 ± 2.0	202 ± 1.0	401 ± 3.3	639 ± 8.1	962 ± 11.2
Widowed and Divorced	161 ± 3.6	89 ± 3.9	246 ± 5.1	432 ± 5.1	692 ± 9.3	1084 ± 7.8

and in other experiments a *reduction* in tumor size was noted in females that were shocked for three days *prior* to virus inoculation. Another study done at Howard University also showed that behavioral stress could be utilized to inhibit the growth and development of transplanted and induced tumors in rats. This type of activity is seen to correspond best to that phase of Professor Selye's general adaptation syndrome known as the "stage of resistance," wherein body defenses are enhanced, and leads us to a consideration of the physiologic mechanisms whereby stress might cause cancer.

A wide range of substances and factors have been implicated in the cause of a variety of cancers. They include irradiation, and cell irritants of a physical or chemical nature, such as asbestos, coal tar, and excessive local heat. However, the two most important agencies which have been shown to exert an influence on the development and subsequent course of malignancy are hormonal activity and the immunologic status of the individual. It is also likely that the central nervous system plays a significant role in the mediation of these important influences. It is therefore, most pertinent to appreciate that these body activities are the most susceptible to the effects of stress, and, indeed, are used as criteria to monitor and characterize the effects of stress in humans.

The hormonal and central nervous system effects of acute stress, with respect to the release of adrenalin and stimulation of the sympathetic nervous system, were first clearly expounded by the great physiologist Walter Cannon in the early 1920's. They were subsequently expanded by the extensive investigations of Selye at the University of Montreal, who demonstrated the role of the pituitary and adrenal cortex in what he termed the "alarm reaction." In recent years, the work of John Mason at the Walter Reed Army Institute of Research (now at Yale University) and others has indicated the participation of other pituitary hormones in this response, notably prolactin (the growth hormone) and agents influencing thyroid and sexual function. Other studies on the release of neurohumoral agents in the brain and newer work on the prostaglandins will undoubtedly further enlarge the scope of hormonal participation and mediation of the response to stress.

We read daily about the possible role of hormones as causative factors in cancer of the breast and uterus. The use of various sex

hormones to treat these lesions and cancer of the prostate are well known. Studies of estrogen receptor activity are now performed routinely on breast cancer tissue removed at surgery to determine the appropriateness of hormonal manipulation as a mode of treatment. Similarly, removal of certain hormone-forming organs is also utilized in the management of a variety of malignancies. Other adrenal-cortical type hormones such as cortisone are also employed in many chemotherapeutic programs. It is clear that the major effects of stress are demonstrated by changes in hormonal activity and, on the other hand, changes in hormonal activity have powerful influences on the malignant process, thus completing that link.

One of the current theories of how cancer starts states that tumor cells of a malignant nature are constantly present through our system. In susceptible individuals, such cells are able to implant themselves and multiply into malignant lesions, while other persons exhibit a natural resistance to such implantation. This may have to do with the body's ability to recognize and destroy these cells—a function of the immune system. When the organism is exposed to a foreign agent like a virus (measles, hepatitis, polio), it responds by manufacturing antibodies, which have the specific property of combatting or increasing resistance to the offending agent. That is why it is rare to have more than one attack of such virus infections as German measles. This property is exploited as the basis of various immunization techniques in which the susceptible patient is exposed to an attenuated form of the virus, to which he then reacts by creating sufficient defenses through his immune system to thwart a subsequent infection by the same or similar agents. For instance, the eradication of smallpox came about through the observation that by vaccinating children with small amounts of the cowpox virus (which produces only a slight local reaction in man), this initial exposure would stimulate the formation of antibodies to the closely related—but much more virulent and deadly—smallpox virus.

Conversely, loss of the body's immune mechanism is associated with an increased susceptibility to, and rapid spread of, infectious processes. The herpes simplex virus, which is apparently constantly present in the cell, is usually quiescent; but when

resistance is lowered, clinical appearance is manifested as sores about the lips and mucous membranes of the mouth. These lesions are commonly referred to as "cold sores" or "fever blisters," implying that they occur during periods of lowered resistance. It is also of interest to note that the clinical appearance of two closely related viruses are linked with cancer. Patients with herpes zoster infection (commonly known as shingles) are thought to exhibit diminished immunologic defenses and have a higher incidence of cancer. Herpes simplex II virus, which is responsible for recurrent genital lesions, is said to predispose to cervical cancer.

Similarly, adrenal-cortical hormones interfere with the body's immune system or ability to make antibodies, and this property is used clinically to prevent rejection of organ transplants and grafts that the body perceives as foreign. When cortisone was first made available, it was noted that many patients who received it for chronic disorders such as rheumatoid arthritis suffered a reactivation of previously quiescent tuberculosis, presumably due to inhibition of a previously effective defense mechanism. The effect of cortisone and other similar adrenal-cortical-type hormones, are clinically recognized as causing a rapid spread of bacterial and viral infections and are generally contraindicated in infection because of this.

Selye's research clearly demonstrated that stimulation of the adrenal cortex was the hallmark of the organism's response to acute stress, and that as part of this "alarm reaction" there was also a marked involution of lymphatic tissue and of the thymus, the major gland of the immune system. Thus, acute stress obviously could cause loss of immune protection.

Psychologists Klaus and Marjorie Bahnson of the Eastern Pennsylvania Psychological Institute have found a strong correlation between depression and decreased immunologic capacity. More recently, workers in Sydney, Australia showed that loss of a spouse was accompanied by marked reduction in immune function two to six weeks after the event, and that this impairment occurred apart from any apparent significant change in hormonal activity, suggesting that such a response may be mediated directly and not require adrenal-cortical participation. Other evidence suggests that interferon—a nonspecific polypeptide which is one of the basic

defenses against virus infections—is also suppressed under conditions of emotional stress.

Thus far, we have reviewed evidence suggesting a strong relationship between certain emotional states such as depression, particularly bereavement or loss of a strong emotional relationship, and subsequent development of malignancy. We have also noted that such factors represent the most potent cause of stress for humans. Studies with laboratory animals similarly show a strong relationship between stress and experimental cancer. It is apparent that the physiologic effects of stress are reflected in the endocrine system and in the immunologic defense mechanism of the body, and that these are probably two of the most important factors in determining susceptibility and resistance to malignant growth. How does this relate to cancer as a "disease of adaptation" and what is meant by this term?

During the latter half of the nineteenth century, the great French physiologist Claude Bernard promulgated the theory that one of the most characteristic features of living organisms is their apparent ability to maintain the constancy of the internal environment (*milieu intérieur*) despite dramatic changes in environmental surroundings. By internal environment, Bernard meant the physical and chemical composition of the fluids that surround the cells of the body. Thus, although the organism might consume large amounts of certain chemicals such as salt, and though the atmospheric conditions might vary, certain adaptive mechanisms came into play designed to preserve the status quo. We all know that regardless of the temperature outside—whether it be 120°F or 20°F—the body temperature tends to remain at 98.6°F as a function of complex adaptive responses. Similarly, when large amounts of sugar are consumed, temporary changes in the concentration of this substance in the blood occur, but various physiologic responses involving the pituitary, adrenals, pancreas, and kidneys rapidly restore blood sugar levels to normal. Loss of such adaptational responses implies illness and portends death.

In the early part of this century, these theories were expanded at Harvard by Walter Cannon, who termed this power to maintain the integrity of the internal environment *homeostasis*, or the *steady state*. Cannon described the changes which occurred when the or-

ganism was severely threatened, indicating that the resultant stimulation of the sympathetic nervous system and release of adrenalin was purposeful and designed to prepare the animal for "fight or flight." The action of adrenalin caused a release of energy stored in the liver with a resultant rise in the blood sugar to provide more fuel for active cells, an increase in the heart rate and a dilatation of blood vessels in critical areas to increase the availability of nutrients and oxygen, a decrease in the coagulability of the blood to minimize hemorrhage, and an increased efficiency of muscular contraction. The pupils dilated to improve vision and a host of other phenomena ensued designed to satisfy functional needs and improve or enhance existing capabilities.

Bernard and Cannon provided the background for the brilliant and revolutionary theories of Hans Selye, who began studying the effects of stress in laboratory animals over 40 years ago. Using a profusion of techniques that embraced biochemistry, steroid chemistry, physiology, experimental surgery, anatomic and microscopic pathology, he carefully delineated the nature of the animal's response to acute stress which he termed the "alarm reaction." This involved marked activation of the pituitary-adrenal axis with the release of hormones such as ACTH and cortisone, marked shrinkage of the thymus and other lymphoid tissues, as well as acute gastric ulcerations. Exposure to prolonged stress resulted in a "stage of resistance," during which the organism's ability to resist the effects of the stressor were enhanced. And finally, if the stress persisted, there ensued a "stage of exhaustion," wherein adaptive and reparative mechanisms gave out. A variety of illnesses followed, or death occurred. This tripartite response, which appeared to be nonspecific and could be induced by a variety of noxious agents, was termed by Selye the "general adaptation syndrome." Discovery that certain disorders such as hypertension, arthritis, and peptic ulcers could be produced in the laboratory as a consequence of stress led to the concept of these illnesses as being "diseases of adaptation."

Implicit in Cannon's and Selye's theories, and most important for our thesis, is the teleologic premise that biologic responses to stress may have had some purposeful significance in primitive times or in lower forms of life but in higher stages have become

inappropriate, and can indeed prove harmful or even fatal. Some of these responses seem useless or superfluous, such as the bristling of the hair on the back of the neck as a concomitant of fear; but on careful reflection, one can see that this mechanism makes the frightened cat seem fiercer, or that stimulation of these same arrector pili muscles provides a vital means of defense for the porcupine. We must also remember that nature often hyperreacts to a stimulus or need by responses that are exaggerated—for instance, the occasional development of disfiguring keloids in scar formation, or the local response to excessive heat as with clay pipe smokers in whom malignancy occurs at the site of injured tissue attempting to repair itself.

A similar phenomenon occurs in evolution. In a previous review of this subject, I have referred to the principle of *opportunism* in evolution, which is best defined as responding to or fulfilling a need with whatever means are available, even if they are not the optimal means or may ultimately prove harmful. In that essay, written over 20 years ago, I used as an example the variation in the development of horns by some 23 species of antelope in the Belgian Congo [now Zaïre]. The marked differences in anatomical configuration and functional effect do not seem to serve any rational purpose, and in some instances are perhaps disadvantageous and prohibitively unwieldy (as in the kudu). In rewriting that article today, I should choose the development of malignancy in man to illustrate this very point.

As one descends the phylogenetic scale and examines lower forms of life, it becomes apparent that the incidence of cancer progressively decreases. Conversely, the ability of the organism to regenerate tissue, organs, or even parts of the body increases proportionately. Among simpler organisms, certain types of invertebrates have the ability to sever parts of their anatomy when irritated; obviously, this capacity has survival value only if the animal possesses an equally remarkable ability to regenerate the cast-off portion from the available cell remnants. The starfish can grow a new appendage and the newt can regenerate its tail. Human beings, however, do not have such regenerative powers. I should like to suggest that the human cancer chromosome—or whatever else one chooses to call it (genome, DNA molecule, or virus)—is the

modern vestige or replica of this regenerative trait which was once vital to the organism's survival and adaptation but now has actually become dangerous to it. Thus, although the primitive cellular response to loss, injury, or irritation is purposeful new growth or regeneration, this capability is not preserved in man, in whom this response can appear as new growth or neoplasia with far more sinister consequences.

To support such an hypothesis, let me point out that recent experiments have shown that if one injects into the limb of a newt chemicals which are known to result in the development of cancer in man, malignancy does not occur. Instead, the newt grows an accessory limb. If the lens of the eye of this animal is removed surgically and similar carcinogenic agents are implanted, again there is no resultant cancer, but instead a new lens is regenerated. In other words, the same stimulus apparently induces either regeneration or malignancy, depending upon the organism's stage of evolution.

Additional corroboration may be found in a recent article in the *New England Journal of Medicine* that has attracted much publicity and which refers to the phenomenon of the "born-again spleen." The authors reported a series of cases of rupture of the spleen in which, although the spleen had been removed surgically, remnants of functioning splenic tissue could be demonstrated many years later, suggesting for the first time that successful regeneration of an organ could occur spontaneously in humans. Apparently, splenic tissue has this capacity, and presumably the regenerative mechanism in this organ does function purposefully. It is therefore not surprising to learn that the spleen is also unique in that is the only organ in humans that does not give rise to primary cancer! It is also interesting to note that accessory spleens—spleniculi—are not uncommon. In very rare cases, several hundred have been present, representing a reversion to a primitive condition in which splenic tissue is not localized in a definite organ but scattered throughout the gastrointestinal tract, so that from the standpoint of comparative anatomy, the spleen retains certain vestigial characteristics from which it may derive such potential.

The leap from physical to emotional loss should not be troublesome, since even in lower forms of life the ability to regen-

erate tissues must involve something more than a simple local response and include, through some systemic humoral or nervous system pathway, participation of the organism as a whole. The phenomenon of loss is quite likely appreciated by the organism via a chemical or humoral messenger or some aspect of stimulation of the nervous system allowing it to mobilize and integrate its activities for reparative processes.

Man is unique in that he responds not only to actual danger but also to threats and symbols of danger. Indeed, such threats, or the anticipation of noxious stimuli, may elicit responses of far greater magnitude and duration than the actual injury itself. One can think of many examples of this: sitting in the dentist's waiting room or chair, a child anticipating a spanking, etc. Similarly, the protective adaptive reaction, when sustained, may itself be far more dangerous and damaging than the noxious agent *per se*. A rise in blood pressure in response to anger or fear may have some useful purpose in animals, but the irritable executive whose blood pressure boils over and who consequently has a stroke in response to some minor vexation is having an inappropriate adaptive response far more dangerous to his life than the original irritant. Quite probably, emotional stress in humans has more profound effects than physical stress, as demonstrated by the Harvard crewing studies. Emotional stress results in adaptive responses which might once have been useful in our evolutionary progenitors but which have now become injurious to us.

It is difficult in our present frame of reference to conceive of cancer as something that might once have been useful or reparative. The cancer patient today is generally avoided by family, friends, and even physicians, and the diagnosis is considered to be an ill omen and tantamount to a death sentence. Cancer conveys the fear of prolonged pain and suffering, loss of attractiveness and social esteem, or the contemplation of disfiguring surgery—as occurs in neck and head dissection or in a colostomy. The situation is most reminiscent of the Biblical leper who was analogously consumed by a process that was decaying or putrescent. Cancer may indeed be considered obscene in the original sense of that word as defined in the *Oxford English Dictionary*: "offensive to the senses or to taste or refinement; disgusting, repulsive, filthy, foul, abominable, loathsome." The distinguished psychiatrist Karl Menninger

noted that "the very word 'cancer' is said to kill some patients who would not have succumbed (as rapidly) to the malignancy from which they suffer." The euphemism "moon children" has replaced "cancer" in astrological charts. Even a Federal Law—the 1966 Freedom of Information Act—singles out cancer as the only disease exempt from disclosure, since it would be an "unwarranted invasion of personal privacy."

The term "cancer" is Latin, derived from the Greek *karkinos*, both meaning "crab," and according to Galen so called because the swollen veins surrounding the affected part resembled a crab's limbs. Many other interpretations relating to the crab have been assigned to cancer: for instance, its ability to move quickly and silently in all directions, or its similarity to the pincer-like action of the crab claw in eating away tissue; these, however, have no etymological basis. The dictionary defines it as "a malignant growth tumor in different parts of the body that tends to spread indefinitely and to reproduce itself as also to return after removal." The earliest English reference I can find is a quotation dating back to 1601: "Cancer is a swelling or sore comming of melancholy bloud, about which the veins appeare of a blacke or swert colour spread in manner of a creifish clees [crayfish claws]." How appropriate that the adjective "melancholy" should have been used. The symbolic aspects of the term are deftly explored in Sontag's current best-seller, *Illness as Metaphor*.

Does any of this have any practical significance in terms of the prevention of cancer? I think so. It should be possible with the discoveries we have discussed and with further refinements in psychological testing to identify a population that is at greater risk for certain types of cancer—an identification facilitated by a knowledge of predisposing heredity and environmental factors. If hormonal and immunologic alterations play a role in the development and course of certain malignancies, it should be possible to pinpoint those changes and utilize them for predictive purposes; indeed, this is already being done in cancer of the breast and uterus. Similarly, if such factors play an active role in the development of the process, it may be possible to alter them artificially with beneficial consequences. The Nobel laureate Rosalyn Yalow recently noted that the pituitary hormone ACTH is found in virtually all primary lung carcinomas, irrespective of cell type. Perhaps deter-

mination of plasma ACTH may have a role in the clinical management of this disease. Parenthetically, what is the significance of this finding in the light of our knowledge of the importance of ACTH in the responses to stress and the growing evidence that stress may play a determinant role in the development of lung cancer in cigarette smokers? If depression plays a major role in the development of carcinoma, perhaps the development of objective chemical tests to identify such an emotional state could prove extremely useful.

More importantly, if stress or noxious influences can cause cancer, why cannot their antithesis have the opposite effect, as has been suggested for other diseases of adaptation? Adam Smith's *Powers of Mind* cites, for example, the interesting case of Norman Cousins, the distinguished editor of the *Saturday Review of Literature*, who was crippled with a severe and progressive form of arthritis. Having read Selye's work, Cousins reasoned that he could reverse the process by reversing noxious stimuli and apparently "laughed himself well." Several years ago, J. I. Rodale, the founder of *Prevention*, wrote a book entitled *Happy People Rarely Get Cancer*. Why is it that nuns, Mormons, Christian Scientists, and Seventh-Day Adventists have less cancer? Is it because they have found some inner peace or life style which insulates them from stress?

Finally, there is increasing evidence that the patient's emotional participation may play an important role in the course of his disease. This is emphasized in LeShan's book, *You Can Fight for Your Life*, and more recently by the Simontons, who are particularly interested in visual imagery and utilization of techniques such as biofeedback and hypnosis. In a recent publication, they report that during a four-year period, they treated 159 patients with "medically incurable" malignancies and average life expectancies of a year. They claim that of those who have died, the average survival time was over 20 months, and of the 63 surviving, 22% had "no evidence of disease" and tumors were regressing in 19%. Treatment centers utilizing the Simonton technique are now springing up all over the country. If such a biofeedback technique does have merit, then it can certainly be refined and improved.

Biofeedback has been demonstrated to be of significant value where the patient has an immediate opportunity to discern whether or not certain emotional states or thoughts are producing

a desired effect. Thus, connected to an appropriate sensing and recording apparatus, the individual may determine whether thinking one way or another causes his blood pressure or pulse or skin temperature to rise, determinations he would not be able to make under normal circumstances in which there is no tangible evidence that the desired effect is being achieved. The situation is analogous to being placed in a car blindfolded on a racetrack and having to drive completely around the track without any interference. This would be an extremely difficult task; but if the driver had a set of earphones and received a signal in the left ear if he were getting too close to an impediment on the left, or a similar signal in the right ear if some danger were on the right, he could probably negotiate the course very satisfactorily. That is the type of assistance and reinforcement that biofeedback provides. With increasing use and experience, one could probably learn to circumnavigate the course at relatively high speeds.

It is known empirically that such emotional states as tranquility or relaxation are associated with a reduction in blood pressure. This provides a basis for using such techniques as transcendental meditation or the relaxation response to lower blood pressure. In this approach to cancer therapy, however, there would not appear to be the same degree of quantitative or qualitative effectiveness as formal biofeedback techniques provide. Mental imagery techniques and changing of the patient's attitude may very well be steps in the right direction, but what is needed is a more precise means of measuring whether or not the desired result is being accomplished. Otherwise, one is very much like the blindfolded racetrack driver.

There are certain nonspecific markers for malignancy such as the carcinoembryogenic assay, and other more specific indicators for certain types of cancer such as acid phosphatase for cancer of the prostate. No one knows exactly how rapidly these fluctuate with the state of the malignant process; but if it were possible to monitor the activity of malignancy by some such objective criterion, then the efficacy of such imagery or other biofeedback techniques would be greatly enhanced.

There are many claims for cancer cures, all with their zealous advocates: mineral waters, comfrey and other herbs, voodoo, yoga, faith healing, krebiozen, acupuncture, laetrile, and various

shrines. It would seem unreasonable to state that there is not a scintilla of truth in any of these claims, and yet it is perfectly obvious that none of these agencies is consistently effective. What could they have in common?

The clue may be found in the case history cited by Klopfer in his description of a patient with a far advanced lymphosarcoma who begged to be treated with krebiozen. Following the initial administration of this substance, his tumor masses "melted like snowballs on a hot stove." Where previously he had required an oxygen mask to breathe, he was now able to fly a plane at 12,000 feet without any effort. However, after some unfavorable publicity appeared suggesting that krebiozen was ineffective, he again became bedridden. His physician, in desperation, then told him the reports were inaccurate and based upon deteriorated preparations of the drug, and that he would be given a stronger dose of a more active potent principle. Actually, he was given *distilled water*, but again the disease disappeared rapidly. When, however, it was announced that the Food and Drug Administration and the American Medical Association had found krebiozen to be worthless, he thereupon succumbed to his disease within a matter of days.

In a discussion in one of the papers presented at the New York Academy of Sciences International Conference on Immunology of Cancer, reference is made to the "Berkley-Smythe effect" noted at McMaster University in Toronto in a study utilizing BCG vaccine in patients with lung cancer. The initial program was undertaken by an enthusiastic thoracic surgeon given the pseudonym "Berkley-Smythe," who had a positive, personalized, optimistic approach and achieved rather remarkable results. Because of this, the study was, subsequently, greatly expanded but now carried out by different staff physicians. Surprisingly, absolutely no improvement was noted in the new group of patients. I should like to quote from the discussion:

> We then sat down and said, why is this? Why are we seeing no beneficial effect? Why did the first four patients do so much better? We said, let's try to visualize the patient who is in the cubicle when Berkley-Smythe walks in and says, "Good afternoon, Mr. Featherwick. It's good to see that you've recovered from your operation. You are feeling much better now, aren't you? Mr. Featherwick says, "Oh yes, I'm feeling a hell of a lot better than I did when I had my chest

tube in, and I really feel like I'm on the road to recovery." Berkley-Smythe then agrees that he's doing very well, indeed, but that his outlook might be even better with some additional treatment. "We now have a good way to treat you that we've learned about from experimental animal studies and from other people's work with patients who have a similar problem to yours. We would be glad to do this for you if you would like to try it; wouldn't you Featherwick? OK, just sign this consent form. You know it's a pretty benign treatment. There are some complications that could occur, but they aren't nearly as bad as the operation that you came through well." All of which is true. So the patient is entered into the study and comes back every visit to see Berkely-Smythe, who is smiling and enthusiastic, and the patient is smiling enthusiastically and doing well.

On the other hand, there are doctors in the immunotherapy clinic who don't have the aura of Berkley-Smythe. Dr. Marvin Milquetoast is one. Marvin goes to see a patient (let's call him Mr. Thanapolensis) whom he has never seen before and introduces himself as Marvin Milquetoast, the immunotherapist. "Your doctor," says Marvin, "has referred you here for our experimental treatment protocol. Now, we really don't have any idea whether this treatment is any good or not, but there isn't much else we can do for you, so we'd like to include you in this experiment. You may get the treatment or you may not, but if you'd like to join anyway and maybe get a chance at it, we'd be happy to have you. Before you sign, though, I have to tell you that you'll get sores on your arms and legs, you may get a fever or throw up, and you may get granulomatous hepatitis, or even anaphylaxis and die. But you'll probably be okay. Now you understand that, don't you?" So Mr. Thanapolensis signs up, and away we go. But somehow, Dr. Milquetoast's patients don't do very well.

We've all seen in one way or another this phenomenon, which I have termed the Berkley-Smythe effect, the powerful influence of psychologic suggestion. We have recently learned that it is sometimes possible to convince a patient to lower his own blood pressure. Maybe it is even possible that psychologic forces might help a patient to subdue his own tumor. We also see the Berkley-Smythe effect acting on ourselves and other investigators, and I think we must be very careful that it does not influence our objectivity, particularly as we report our results in meetings like this one.

Both of these anecdotes are strongly reminiscent of a well-recognized phenomenon in clinical medicine known as the "placebo" effect, which is generally acknowledged but poorly understood. It must in some way activate whatever self-regulatory mechanisms lie latent in the body as a factor in the expectation or hope of cure. It seems likely that such a compelling belief, hope, or trust is also the basis of those unusual instances of sudden remis-

sion from cancer for which there is no rational explanation. (I do not include vitamin C in the list of the above placebo-type "cures" because there is increasing evidence that this substance may play an important pharmacologic role in the therapeutic management of malignancies, and the profound effects of stress on vitamin C metabolism makes such a relationship plausible.)

The National Cancer Institute estimates that 80-90 percent of human cancers are attributable to environmental carcinogens; and this, of course, implies that cancer is largely preventable, and quite likely, a disease of man-made origin. *The New York Times* (June 17, 1978) quoted the Director of the National Cancer Institute as conceding that "a rosy view of the cancer problem is unwarranted." He suggested that more money ought to be spent on preventing cancer by changing the environment, and less on "unproven hypotheses" such as that cancer is caused by viruses. The next day's paper carried a page-one article indicating that spiritual healing was gaining ground among Catholics and Episcopalians, citing certain cancer patients "who recovered or enjoyed long remissions, or whose final days were painless."

I find an appealing link between these two items because they refer to both the external and internal environment and raise important questions. Hardly a week goes by that we do not find some report of epidemiologists studying an outbreak of cancer in a certain locality or among a specific group of individuals. Epidemiology attempts to deal with certain basic questions as to where a given disease is found, where it flourishes and when and where it is not found. Professor Danishevsky of Moscow divided epidemiologic climates into two categories: a so-called "macroclimate" which has to do with measurable factors such as temperature, humidity, atmospheric pressure, and air pollution, and a "microclimate" which represents the sum of the intimate sociologic, spiritual, and habitational conditions in which a given individual finds himself. As we shall see, there is a strong support for the position that cancer appears to be a disease of civilization and environment, and it may be more related to the "microclimate" than the "macroclimate."

The renowned medical missionary, Dr. Albert Schweitzer, wrote:

> 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. . . .

The celebrated anthropologist and Arctic explorer, Vilhjalmur Stefansson, in a book entitled Cancer: *Disease of Civilization?*, noted the absence of cancer in the Eskimos upon his initial arrival in the Arctic, but a subsequent increase in the incidence of the disease as closer contact with white civilization was established. He quotes Sir Robert McCarrison, a physician who surveyed 11,000 Hunza natives in Kashmir from 1904-1911, and concluded that cancer was unknown among them. In addition to their diet, the Hunzas were "far removed from the refinements of civilization. Certain of these races are of magnificent physique, preserving until late in life the character of youth; they are unusually fertile and long-lived and *endowed with nervous systems of notable stability*. . . ."

Dr. Morley Roberts' *Malignancy and Evolution* (1926) contained the observation: "I take the view commonly held that, whatever its origin, cancer is very largely a disease of civilization," and he was referring to a wide body of literature, such as Dr. Charles Powell's *The Pathology of Cancer* (1908) which stated: "There can be little doubt that the various influences grouped under the title of civilization play a part in producing a tendency to Cancer."

The earliest reference I have been able to find to support this thesis is LeConte's "Statistical Researches," in which he quotes the unpublished "Memoir on the Frequency of Cancer" which the French author Tanchou addressed to the French Academy of Science in 1843:

> 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 per 1000 in London! Estimating the intensity of civilization by these data, it clearly follows that Paris is four times more civilized than London!

In an article in the journal *Cancer*, in July 1927, Dr. William Howard Hay wrote:

> A study of the distribution of cancer, among the races of the entire earth, shows a cancer ratio in about proportion to which civilized living predominates; so evidently something inherent in the habits of civilization is responsible for the difference of cancer incidence as 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 of cancer until mixture with more civilized man corrupts the naturalness of habit, and just as these habits conform to those of civilization, even so does cancer begin to show its head. . . .

One of the most impressive arguments is to be found in Dr. Alexander Berglas' work *Cancer: Its Nature, Cause and Cure,* published in Paris in 1957. Throughout this book runs the theme that cancer is a disease from which primitive peoples are relatively or wholly free. Berglas declares: ". . . there is as yet no remedy for cancer; it is not infectious, and it is the most frequent cause of death in highly developed countries (exclusive of death due to wear and old age); . . . everyone of us is threatened with death from cancer because of our *inability to adapt to present day living conditions*." It is in his Preface, however, that I find the most significant, prophetic and useful commentary:

> Over the years, cancer research has become the domain of specialists in various fields. Despite the outstanding contributions of the 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, had the peculiar result of becoming an obstacle to the study of 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.

The current thrust of cancer research appears to be in the area of environmental carcinogens, especially those of dietary or atmospheric origin. In addition to such an epidemiologic approach, what is required is an endemiologic investigation, the search for common factors that lie *within* the affected population. What is

needed is a new breed of physician, fluent not only in the technical and scientific advances that medicine has to offer in physiology, biochemistry, and psychology, but equipped with a sufficient background in literature, history, philosophy, and the humanities to enable him to evaluate the individual from a truly holistic viewpoint.

There is sometimes a tendency to minimize the significance of observations made by earlier investigators because they lack "scientific proof" or "statistical significance," but I have emphasized the opinions of 18th- and 19th-century physicians in this presentation since these doctors undoubtedly enjoyed a doctor-patient relationship that is not often seen today. By virtue of their own cultural background and their freedom to spend more time with their patients, their perception and appreciation of the significance of developmental and personal environmental factors were indubitably enhanced. Indeed, "it is sometimes much more important to know what kind of patient has the disease than what kind of disease the patient has."

Louis Pasteur, who was preoccupied with microbes as a cause of disease, had many debates with his contemporary, Claude Bernard, who, as we have seen, stressed the importance of the body's own equilibrium and the significance of the *milieu intérieur* or internal environment. It is reported that on his deathbed Pasteur said: *"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.] In other words, the type of patient may be more important than the nature of the disease in determining the outcome.

Sir William Osler, possibly the greatest of all clinicians, used to tell his students: "Show me what goes on in a man's head, and I will tell you what will become of his tuberculosis," and that was long before we knew anything about a drug called cortisone, which promotes the rapid spread of tuberculosis, or before we had discovered that hormones such as this were the hallmark of the response to stress. Significantly enough, he also observed that faith was the physician's greatest aid.

The causal relationship between stress and numerous disorders has been increasingly accepted since Selye's revolutionary concept of "diseases of adaptation." There is no longer any doubt

that stress can influence all human disease. Its relationship to cancer may be difficult to "prove" to a statistician's satisfaction, for reasons noted above, but that does not exclude the possibility or likelihood that it will soon join the ranks of what might be more appropriately relabeled "diseases of maladaptation."

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