HEALTH AND STRESS

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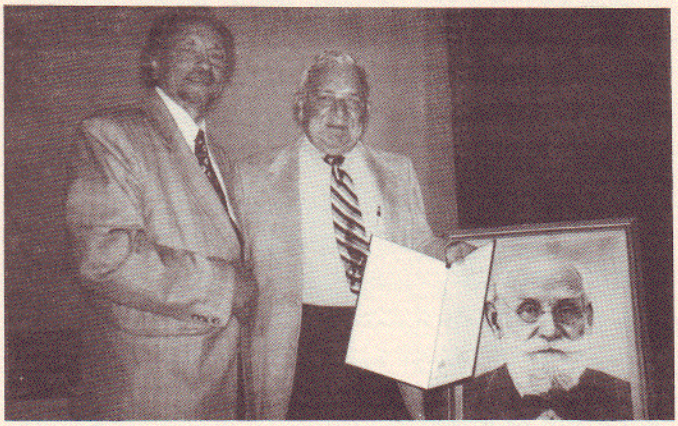
CAN MENTAL STRESS CAUSE CANCER?

Key Words: Descartes, Cannon, "fight or flight", General Adaptation Syndrome, cancer as an attempt at regeneration in response to loss, Cancer, Stress, And Death Symposium, immune sytem response to loss,, teleology

The notion that certain mental states or personality traits could contribute to cancer can be found in our earliest medical writings. The ancient Greeks taught that there were four humors - yellow bile, black bile, phlegm, and blood. It was believed that these humors contained thoughts and feelings that were constantly circulating through the body, exerting their effects by direct physical contact with particular parts of our anatomy. Each humor was associated with either heat, cold, moisture, or dryness, as well as a certain personality.

In healthy people, these four humors were in equilibrium. When this balance was upset, different diseases could occur, depending on whether there was an excess or deficiency of a particular humor. Treatment involved correcting the corresponding abnormalities in temperature and/or humidity that had resulted.

Two thousand years ago, the Greek physician Galen noted in *De Tumoribus*, his treatise on tumors, that cancers of the reproductive organs were particularly apt to occur in women who were melancholy because they had an excess of black bile (Gr. *mélas chole).* Galen's humoral theory of disease dominated Western medicine until just a few hundred years ago, but vestiges remain. People are still described as being "melancholy", "bilious", "phlegmatic", "sanguine", having a "dry" sense of humor", being "all wet", "hot headed" or "hot -blooded". Some of these traits are associated with certain disorders, and recent research confirms Galen's suspicion of a link between depression and cancer.



Professor Konstantin Sudakov congratulates Dr. Paul Rosch on his election to the Russian Academy of Medical Sciences on the occasion of Pavlov's 150th birthday. Dr. Rosch's invited presentation was on " Stress And Cancer: Diseases of Communication, Control and Civilization".

ALSO INCLUDED IN THIS ISSUE

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Hans Selye's Diseases Of Adaptation

The ancient Greeks and other cultures believed that mind and body were inseparable, and that emotional distress could result in physical illness. However, Western medicine came under the influence of the 17th century French philosopher-mathematician Rene Descartes. He viewed the body as a complex machine. Illness resulted when one of its parts failed to function, and it was the physician's job to identify the problem and fix it. Disturbances of the mind, Descartes said, were entirely separate, beyond man's ken, and belonged in the province of the Church.

It was not until the present century that things began to change. Walter Cannon had shown that when laboratory animals were suddenly subjected to severe threats, there was an outpouring of adrenaline and stimulation of the sympathetic nervous system. This caused a cascade of what he called "fight or flight" responses designed to preserve life. Increased tension in the large muscles of the extremities provided greater strength in physical combat or speed to get away from a scene of potential peril. A rise in blood sugar furnished more energy, higher heart rate and blood pressure increased circulation in the brain to facilitate decision making, pupillary dilatation improved range of vision, etc., etc.

The advent of psychiatry as a medical specialty led to a new understanding of mental and emotional disorders that required treatment by physicians rather than priests. Pioneers in psychosomatic medicine proposed that ulcers, colds, hypertension, asthma and other diseases could result from emotional stress. However, the first scientific proof of this came from Hans Selye, a brilliant Canadian researcher, who essentially coined the term "stress" as it is currently used. He had demonstrated that when laboratory animals were subjected to extremely noxious emotional or physical stimuli for several hours, they consistently developed gastric ulcerations, shrinkage of lymphoid tissues, and enlargement of the adrenals. This was due to intense pituitary stimulation of the adrenal cortex and increased secretion of cortisone-like hormones.

Selye called this initial response the "Alarm Reaction", and viewed it as a summoning up of the body's defenses. If he continued to subject the animals to noxious stimuli, they seemed to enter a "Stage of Resistance" during which defense mechanisms were maximized. More prolonged and persistent exposure resulted in a "Stage of Exhaustion" that eventually ended in death. Autopsy studies during various phases of this three phase response, which he referred to as the "General Adaptation Syndrome", revealed pathologic findings that seemed identical to those found in patients with peptic ulcer, myocardial infarction, nephrosclerosis, inflammatory arthritis, hypertension, and other disorders. He viewed these as "Diseases of Adaptation", and reasoned that if stress could produce these in his animals, perhaps the stress of civilization played a role in their human counterparts.

Selye subsequently found that by dietary manipulation such as increasing sodium or decreasing potassium, or injecting hormones like desoxycorticosterone prior to exposing the animals to stress, he could selectively produce different disorders, or make the pathologic picture more severe. However, in none of his thousands of experiments was there any evidence that stress caused cancer, or gave rise to microscopic premalignant changes.

Is Cancer A Disease Of Adaptation?

I was very fortunate to have been awarded a Fellowship at Selye's Institute For Experimental Medicine and Surgery at the University of Montreal shortly after the publication of his magnum opus *Stress* in 1950. We became good friends, and he invited me to co-author several articles including the lead chapter "Integration of Endocrinology" for the *A.M.A. Textbook of Endocrinology*. We maintained a close personal and professional relationship after I left the research arena to enter clinical practice; although Selye never saw or treated a patient, he referred many to me. From time to time he would also ask me to fulfill writing or speaking assignments that did not fit into his schedule.

I was surprised when he called me in 1976 to indicate that his International Institute of Stress and the Sloan-Kettering Institute were planning a symposium entitled "Cancer, Stress, and Death" in Montreal. He said that he was coming to New York and would like to have dinner with me to discuss my participation in this symposium. I was delighted to see him again, and we reminisced about many things. He reminded me that 25 years previously, while having dinner at his home in Montreal, I had suggested that cancer might be another one of his "Diseases of Adaptation" to the stresses of civilization. Of particular importance in this regard were bereavement and the loss of important emotional relationships, emotions that would be difficult to reproduce in laboratory animals. Alternatively, cancer might take a much longer time to develop than we had available for follow-up observations.

I had only a very vague recollection of this conversation but he was able to recall it in detail, explaining that he now had a very personal interest in this subject. Five years previously, following a series of very stressful events, he had developed a tumor in his thigh. It was diagnosed as a histiocytic reticulosarcoma, a rare malignancy that is usually fatal. Although he refused chemotherapy and radiation, he made a complete recovery which he attributed to his firm determination to continue living in order to complete his important research.

He now felt strongly that some cancers were indeed related to the stress of contemporary civilization, and conversely, that a strong faith, social support and other stress reduction strategies could retard or reverse malignant growth. He wanted me to present a paper on cancer as a Disease of Adaptation at the symposium which would also appear as a chapter in the Sloan-Kettering Cancer Series. I felt flattered, and it was difficult for me to refuse anything that Selye requested. However, I politely pointed out a number of potential pitfalls. Trying to prove that stress caused cancer in humans would be an exercise in futility for several reasons. There were the usual difficulties in attempting to define and measure stress. In addition, it would be impossible to determine whether a cancer had actually started years, months, or weeks before it was first detected. Animal studies had shown that stress could both accelerate or retard the growth of malignant tumors.

More importantly, I had been completely involved in clinical practice for the past 20 years. I no longer had the time, training, or resources to do a proper job of researching the various aspects of this subject. We reminisced about other things, and I assumed the matter was closed. I drove him to the airport, we chatted some more, and he gave me an affectionate hug as we said good-bye, adding "you'll be hearing from me" as he walked to the plane.

Two weeks later, I received a large packet containing over two dozen reprints dealing with various aspects of stress and cancer ranging from animal studies to philosophical considerations. Selye had underlined various statements and written comments or questions on most that were designed to pique my curiosity. He had done a great job in baiting the hook, as the items were carefully arranged to build up some crescendo effect that made the challenge almost irresistible. There were several references that I was anxious to read based on their titles. He appended a short note asking me to reconsider the assignment after I had a chance to review all of this information, and promised to put his entire library and research staff at my disposal.

The Significance Of Emotional Loss

I was particularly impressed with the observation that prior to the present century, it was widely assumed that cancer was caused by stress. In 1701, Gendron, emphasized the effect of "disasters of life as occasion much trouble and grief" in the causation of cancer. 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". Towards the end of the century, Nunn was impressed with the influence of distress in developing breast cancer and Stern wrote that cancer of the cervix was more common in frustrated females.

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." A few decades later, 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. Numerous other citations attest to the firm belief of 18th and 19th century physicians that emotional stress could cause cancer.

I attach particular importance to these commentaries for several reasons. The most important is the practice of medicine, which in those days was quite different, especially with respect to patient encounters. Physicians had to rely more upon eliciting a detailed history and evaluating the patient's home and work environment, emotional makeup, and social life in arriving at a diagnosis. This is in sharp contrast to contemporary depersonalized diagnostic work-ups, which emphasize sophisticated laboratory tests and imaging procedures. In addition, the education of doctors in those days 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 present prevailing preoccupation with basic sciences at the expense of the humanities.

Physicians of that era spent much more time questioning their patients about intimate family, social and work relationships, and had more of an opportunity to see their living conditions firsthand. They were also apt to be keener observers, and more sensitive to emotional or behavioral characteristics that might relate to patients' complaints. Thus, by virtue of their educational background, more personalized approach and cultural orientation, they would have been much more sensitive to the possibility of some relationship between stress and cancer than is possible in the frenetic pace of today's hurried, hectic, "high tech and low touch", practice of medicine.

Interest in a stress-cancer link was rekindled in this century with the advent of psychiatry as a specialty. Evans, a Jungian psychoanalyst, again called attention to the link between **loss of a close emotional relationship and cancer**. Kissen found similar personality traits in patients with lung cancer that differentiated them from those with other pulmonary diseases and later extended these observations to other malignancies Schmale and Iker were intrigued with the relationship between antecedent stress and cancer of the cervix. 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; this observation has recently been reconfirmed. Greene, a hematologist, carefully studied the life histories of three sets of identical twins, one of whom had died of leukemia. He noted that each twin with the disease had experienced an antecedent emotional upheaval that had not been shared by the survivor. In another 15 year study of patients with lymphoma and 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, depression, or hopelessness.

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Thomas' forty year prospective health study of Johns Hopkins medical students showed that physicians who subsequently developed malignancies often tended to be lonely individuals, who had figuratively "**lost their parent**". Le Shan was impressed with similar characteristics he had often noted in his cancer patients. 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: **the loss of an important emotional relationship**; an inability to express anger or resentment; an unusual amount of self dislike and distress; and feelings of hopelessness and helplessness. Various writers and poets have also commented on the relationship between emotional loss and cancer, including Tolstoy, Auden and Sontag. 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.

The gold standard for measuring stress is the Holmes-Rahe scale, which rates the severity of various life change events. At the top of the list is **loss of a spouse**; significantly higher mortality rates for cancer and other leading causes of death have been reported in bereaved survivors over the following 6-12 months. Several studies have demonstrated concurrent impaired immune function, especially depression of T-cell mitogenic and natural killer cell activity during this time period. 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. Decreased immune defenses have even been reported in **workers who lose their jobs and remain unemployed**.

The unusually low incidence of cancer in schizophrenic patients may be related to their inability to experience the stress normally associated with bereavement or emotional loss. I have emphasized the importance of this type of stress because it may initiate activities that once were useful, but have now gone awry.

Cancer As An Evolutionary Response

As one descends the phylogenetic scale, cancer becomes progressively less common with each lower form of life, and eventually disappears. Conversely, the ability of the organism to regenerate injured or lost tissues increases proportionately. Simple organisms have the ability to completely regenerate parts of their anatomy if they are lost. A starfish can restore a lost appendage, and even a newt will grow a new tail or leg if it is cut off. Some organisms have the ability to sever parts of their anatomy when they are injured, e.g. the newt can cause the mechanical release of its tail to escape a predator. 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. This restorative capability is retained in humans only for the first two years of life. If the distal phalanx of a finger is severed before the age of three, nothing need be done, since it will regenerate perfectly, nail and all.

In my chapter for the Sloan-Kettering book, I postulated that some human malignancies are vestigial remnants of this primordial and purposeful, regenerative trait. When we suffer a loss or injury, similar mechanisms are activated in an attempt at regeneration, or repair. Unfortunately, this new growth, or neoplasia, can prove to be harmful rather than helpful. This is certainly true for some physical injuries. Cancer of the lip often developed in clay pipe smokers, in an attempt to repair heat damaged tissue. People who carried braziers of burning charcoal or coal developed skin cancers at sites where these metal containers made contact.

Experiments with chemicals that cause cancer when applied to the skin support the hypothesis that some cancers are the counterpart of regeneration of healthy, normal tissue in lower forms of life. When these carcinogens are applied or injected into the leg of a newt, a tumor does not form. Instead, a new accessory limb will start to grow at that site. If the same carcinogen is injected into the epithelial iris tissue of the eye, the newt will regenerate a new lens.

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Thus, the identical stimulus can produce either purposeful regeneration or a malignant growth, depending upon the evolutionary development of the organism. 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 centers could initiate coordinated restorative activities, most likely involving the integration of neurohumoral, and immune system mechanisms. With man's highly developed cere bral cortex, emotional loss might well be perceived as being an even greater stress than some physical loss, for which a substitute was available. The same reparative signals may be activated, but our responses are anomalous and aberrant. Our strivings to stimulate purposeful replacement are futile and fruitless. Any resultant new growth is apt to be in the form of neoplasia that is malignant because of **problems in communication** that lead to a **loss of control** of the mechanisms that normally govern cell growth.

Selye was unusually enthusiastic about my hypothesis, and commented on it 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 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"

I have written a great deal about the role of communication and control since then, particularly with respect to how an appreciation of these influences can provide insights into the mechanisms underlying well docu mented cases of spontaneous remission of cancer. However, the title of my recent talk in Moscow was " Stress And Cancer: Diseases of Communication, Control and Civilization". What has civilization got to do with cancer?

Is Cancer A Disease Of Civilization?

In keeping with Selye's assignment, my presentation dealt with cancer as a "Disease of Adaptation", but in retrospect, "Disease of Civilization" might have been a more appropriate subtitle. This may suggest some allusion to smoking, air pollution, exposure to asbestos, and other cancer causing substances in the environment, depletion of the ozone layer, radiation hazards, and other current carcinogenic concerns. However, what I am referring to are psychosocial stresses that were evident long before these 20th century problems. This concept is not new, and was proposed over a century and a half 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".

In *The Cancer Problem*, Bainsbridge wrote "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.**"

Hoffmann's *The Mortality of Cancer Throughout the World*, a global survey conducted for The Prudential Life Insurance Company, emphasized that cancer was rare in primitive peoples and was related to civilized life styles.

> "In the opinion of qualified medical observers, cancer is exceptionally rare among the primitive peoples including the North American Indians and the Eskimos. " The rarity of cancer among native (primitive) races suggests that the disease is primarily induced by the conditions and methods of living which typify our modern civilization."

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The African medical missionary, Dr. Albert Schweizer; substantiated this:

> "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."

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, and a subsequent increase in the incidence of the disease as closer contact with white civilization was established. Both Schweizer and Stefansson emphasized that this was not related to any dietary alteration, but rather a change in life-style. Sir Robert McCarrison, a physician who carefully studied thousands of Hunza natives in Kashmir from 1904-1911, confirmed their unusual longevity, ability to retain a youthful appearance well into their sixties or seventies, and an absence of cancer. He attributed this to the fact that they were "endowed with a nervous system of notable stability" (stress resistant), and were "**far removed from the refinement of civilization.**"

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

> "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 compete absence until mixture with more civilization, even so does cancer begin to show its head."

In *Malignancy and Evolution*, Roberts wrote, "I take the view **commonly held** that, whatever its origin, cancer is very largely a **disease of civilization**". Moore's *The Antecedents of Cancer,* also "**connect the progress of civilization with the increase of cancer, which has remained an incontestable theory** to the present day."

Similarly, Powell wrote in *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." Hooker's *Eclecticism in Cancer Therapy,* urged less emphasis upon research in artificially induced cancer in animals, and more upon the observation of people.

> "There is 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**."

One of the most persuasive arguments is to be found in Berglas' *Cancer: Its Nature, Cause and Cure*. It's prevalent theme is that

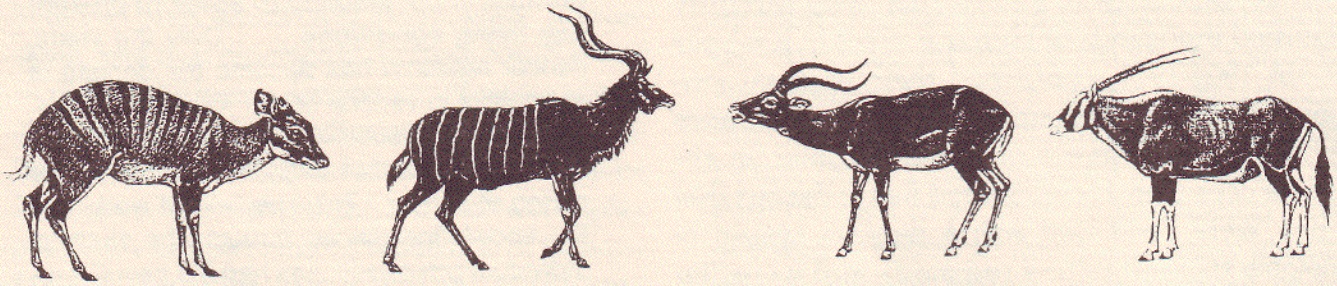
> "Cancer is a disease from which primitive peoples are relatively or wholly free, and that we are threatened with death from cancer because of our **inability to adapt to present day living conditions**. . . . Over the years, cancer research has become the domain of specialists in various fields. Despite 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".**

Cancer is rare in both primitive forms of life and primitive societies. It's incidence rises progressively as species become more highly developed and as civilization becomes more complex. It would thus seem that the incidence of cancer will continue to increase, which seems counterproductive from an evolutionary perspective. However, many responses to stress that seem senseless were undoubtedly purposeful during the lengthy course of human evolution. In other instances, they simply represent the best that can be done with what is available.

"Opportunism" In The Evolution Of Antelope Horns And Cancer

Implicit in Cannon's "fight or flight" theory is the teleologic premise of a purposeful design in all of Nature. Some responses to stress, like cancer, may prove harmful, and many others seem senseless. Nevertheless, all can be shown to have served some useful purpose during the lengthy course of human evolution. When severely frightened, some people feel their "flesh crawl", develop "goose bumps", or the hairs on the back of the neck "stand up". While these don't help us, the "flying fur" on the arched back of an aroused cat makes it appear more ferocious to an assailant. Similarly, the stimulation of these same arrector pili muscles in the porcupine is responsible for its "bristling quills", which provides a very effective defense mechanism. Diarrhea is an embarrassing response to stress, but for an antelope fleeing from a lion, shedding some extra weight could have increased speed.

There are other examples of the *vis medicatrix naturae* (healing ways of nature) going awry, such as the principle of "opportunism in nature". Simply stated, this refers to the ability to meet a need with whatever is available, even if it is not the best available, and ultimately proves harmful. One example of this is the variation in the horns of some 23 varieties of antelope in the Belgian Congo. Horns are their principal means of offense in struggles within the group, and of defense against attack from other animals. There must be one type of horn which is basically the most efficient, yet it is clear that none of these antelopes possess this "best horn". The horns of the duiker are too small to be effective, the kudu's are prohibitively unwieldy; the impala's double curve have the same placement and direction as those of the gemsbock's but are much weaker mechanically and have no advantage. Like the horns of the antelopes, certain cancers could also illustrate the principle of opportunism. If this is this case, then it is meeting the need to respond to loss with whatever is available, even if it is useless or harmful.



DUIKER **KUDU** **IMPALA** **GEMSBOCK**

Further evidence that stress can contribute to cancer comes from research showing that reducing stress through social support or developing a strong faith can retard or possibly even reverse the growth and metastases of malignant tumors. A subsequent Newsletter will deal with possible underlying mechanisms, including the role of religiosity and spiritualtiy, so stay tuned.

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