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The Link Between Psychological Stress and Carcinogenesis

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Abstract

The following research paper examines the correlation between psychological stress and carcinogenesis. A number of studies have indicated that there is a positive correlation between stress and cancer development as well as progression. Results indicated that an extensive longitudinal study is needed in order to definitively conclude that stress has a direct effect on cancer development in humans.

Researchers have determined that when an individual is experiencing stress, physical changes occur within the body. During a stressful situation, "the hypothalamus activates the pituitary gland, which in turn activates the adrenal glands to produce hormones that cause chemical changes in various cells and tissues" (Benson & Stuart, 1992, p. 324). This process is called the fight-flight response. During this fight-flight response, the immune system can become suppressed. The suppression of the immune system leads to susceptibility to diseases, including cancer. Conversely, it has been demonstrated that positive messages from the brain can enhance the ability of the immune system to stave off disease. This mind body connection is referred to as psychoneuroimmunology (PNI).

PNI research began in the 1960s. Today's researchers have become progressively more sophisticated. PNI Researchers examine how psychosocial factors such as optimism and social support moderate stress responses. "They are mapping the biological and

cellular mechanisms by which stress affects the immune system, and they are testing new theories, such as the idea that the immune system acts as a "sixth sense" that gives the brain valuable information about a person's health status" (DeAngelis, 2002).

One of the newest theories of PNI is called the bi-directional model. It states that there is a link from the immune system to the brain and not the other way around. According to this theory the immune system is a messenger that signals the brain to infection or injury by releasing proteins called proinflammatory cytokines. These cytokines travel to the central nervous system and brain to communicate information about the body's distress. Next, "the brain releases its own cytokines that signal the central nervous system to initiate a surge of responses such as fever and listlessness that, theorists believe, help the body adapt by reducing energy output" (DeAngelis, 2002). PNI researchers are interested in cytokines because they epitomize an immune response gone wrong. Stress increases hormones, which slow the delivery of cytokines to the site of injury or infection.

Robert Ader, an experimental psychologist, was interested in the psychosomatic characteristics of disease. On the 45th day of Ader's taste-aversion experiment, a few of the rats he used

had died. A few more rats died in the next few days. Ader had conditioned the rats to have an aversion to the taste of saccharin. Ader used a chemical called cyclophosphamide, which causes nausea in rats. Ader gave the rats an injection of this chemical, and immediately afterwards, he would give them a saccharin-flavored drink. After 50 days, the taste-aversion was extinguished and the experiment ended. Ader wanted to know why the rats had died. When he researched the properties of cyclophosphamide, he discovered that it suppressed certain reactions of the immune system.

Ader had unintentionally produced a situation in which the rats were conditioned to weaken their own immune systems (Dacher, 1991). According to Ader's theory, the rats had associated the saccharin with both the nausea inducing effects and immune suppressing effects of cyclophosphamide. Due to this psychological pairing, every time a rat took a drink of the saccharin alone, it thought it was cyclophosphamide and nausea and immune suppression followed.

Ader learned that the rats that died were the ones that drank the most saccharin flavored liquid. Ader inadvertently taught the rats to do on their own, what the cyclophosphamide did. This experiment demonstrated that the immune system could

be influenced by what an organism believed and what went on in its brain.

In the past decade, psychobiologist Shamgar Ben-Eliyahu has been working on the link between stress and tumor development.

Ben-Eliyahu and his colleagues discovered that stress such as "forced swim, surgery, and social confrontation decreases lymphocyte activity in rats for as little as one hour and as long as a day or two" (Azar, 1999). These types of stresses also cause a two-to-five-fold increase in certain types of tumors. These stresses also advance tumor growth.

Emory University psychologist Jay Weiss found evidence that b-lymphocytes (the type of white blood cell that responds to an antigen by producing antibodies) are involved in combating tumor cells in the lungs of rats. According to Weiss, b-lymphocytes are the immune cells that are most influenced by stress.

Another study investigated the possibility that stress could weaken one part of the DNA repair process. Forty-five rats were given dimethylnitrosamine (a carcinogen), and half were assigned to a stress condition. The methyltransferase, a DNA repair enzyme generated in reaction to carcinogen damage, was drastically reduced in stressed animals' splenic lymphocytes, as compared with splenic lymphocytes obtained from the control rats (Kielcot-Glaser & Glaser, 1999).

Experiments on immune system suppression and psychological stress are not limited to lab rats. Janice K. Kiecolt-Glaser and her colleagues conducted a series of experiments on medical students in 1985. "Glaser and her colleagues documented that commonplace stressful events resulted in immune suppression as detected in students' blood samples taken during examinations as compared to similar samples taken one month previously" (Dacher, 1991, p. 22). These findings demonstrate that anxiety (like the anxiety involved with test taking) could affect the immune system.

Bereaved spouses are another example of stress and immune system suppression. "Bereaved spouses, and most particularly widowers, are significantly more vulnerable to disease than the unbereaved" (Pearsall, 1987, p. 104). Lymphocyte responsiveness (the effectiveness of the part of the immune system that fights disease by maintaining homeostasis and preventing over production of cells) decelerates in a person who has lost a partner. When these lymphocytes were stimulated with mitogens (a substance that induces mitosis, or cell reproduction) "they reproduced at a significantly lower rate than those of individuals who had not lost a significant person in their lives" (Pearsall, 1987, p. 104).

It is a known fact that lymphocytes have minute receptors on their surface intended for the reception of a range of secretions from the brain so that they can operate in response to the brain's signals. It is possible that the loss of daily interactions and closeness can cause the brain to signal the body cells to develop more rapidly than normal in order to fill that void of activity. This would make the lymphocytes less effective due to the chemical changes, which hinder the response at receptor sites. This causes cell disease to begin. This theory of cell disease is called surveillance theory of cancer (Pearsall, 1987). This theory holds that cancer cells are constantly developing in the body, but that the immune system's ability to recognize them as abnormal and destroy them are what prevents them from becoming malignant tumors. When the number of cancer cells becomes too large to be destroyed or when the lymphocytes become suppressed is when carcinogenesis occurs.

Another theory of cancer development and stress involves something called the Type C personality. Just as the Type A personality tends to develop heart problems, the Type C personality tends to develop cancer.

Lydia Temoshok, a psychologist, and her graduate student, Andrew Kneier, conducted a study at the University of California. Temoshok and Kneier compared the responses of

patients with malignant melanoma and patients with cardiovascular disease to receiving mild electrical shocks. "The patients with malignant melanoma had a stronger physical reaction to the test, but tended to downplay how emotionally upset they were about it when they talked to the researchers afterward" (Goleman & Gurin, 1993, p. 88). Temoshok coined the term Type C personality.

The Type C personality characteristics consist of:

1. The suppression of strong emotions
2. Compliance with the wishes of others and a lack of assertiveness
3. Avoidance of conflict or behavior that might offend others
4. A calm, outwardly rational and unemotional approach to life
5. Obeying conventional norms or behavior and maintaining the appearance of niceness
6. Stoicism and self-sacrifice
7. A tendency towards feelings of helplessness or hopelessness (Martin, 1997).

In a study conducted in the 1960s, women undergoing cervical smear tests were given interviews before the outcome of their tests were known. The results illustrated that women who

expressed feelings of hopelessness during the interview had the greatest probability of being diagnosed with cancer.

In the 1960s, Ronald Grossarth-Maticek started a long-term prospective study of 1,353 Yugoslavian villagers. He learned that the villagers who scored highly on measures of anti-emotionality and rationality were at the most risk for developing cancer. Hans Eysenck worked with Grossarth-Maticek and discovered that personality variables and psychological stress have an important connection with the risk of dying from cancer years later.

In another study, patients with stage one and two malignant melanoma who received no treatment other than surgery, were divided into two groups. One of the groups received psychological support, learned how to use relaxation techniques, received stress management training, and had health education in a six-week period. The second group did not receive such support. The group who received support demonstrated less stress and improved immunologic functioning. Six years later, a follow-up study was conducted on the two groups. The group that received support had a nine percent mortality rate compared to the other group, which had a 17 percent mortality rate. The group that received support also had a 21 percent tumor

recurrence compared with 38 percent in the group that did not receive support.

According to a study in the Journal of the National Cancer Institute, cortisol secretion has an effect on survival time with breast cancer. Cortisol is a stimulatory stress hormone. During times of stress, the sympathetic nervous system (SNS) releases corticotrophin-releasing hormone (CRH). The SNS activates the adrenal glands, which release epinephrine and norepinephrine. Epinephrine and norepinephrine mobilize the body for the fight-flight response. The CRH activates the pituitary gland to release adrenocortico-tropic hormone (ACTH). ACTH activates the adrenal gland to release cortisol. After the stressful event, cortisol halts the production of epinephrine and norepinephrine. This brings the body back to its homeostatic state.

Women with breast cancer had their saliva tested for cortisol levels four times in a 24-hour period. This allowed researchers to examine the circadian rhythm of cortisol release in the women. Circadian rhythm is the body's internal set of clocks, which control sleep patterns. Cortisol levels normally are at their highest in the morning in order to produce

wakefulness. At night, cortisol levels decrease dramatically, allowing for relaxation to induce sleep.

The study found that women who had an abnormal pattern of cortisol secretion had a significantly decreased survival time. This abnormal pattern involves a low level of cortisol secretion in the morning, and a higher level of cortisol secretion at night. The total amount of cortisol secreted did not affect their long-term prognosis. Researchers concluded, "dysregulation of cortisol is associated with more rapid breast cancer progression" (Diurnal, Kraemer, Sapolsky, Sephton, & Speigal 2000).

An abnormal cortisol secretion rhythm implies an out of kilter stress response associated with "poorer sleep patterns, loss of marital and social support, and increased sensitivity to stressors, all of which may affect survival rates" (Diurnal, et al.). Cortisol also suppresses immune response, reducing lymphocyte activity.

A study conducted using 28 psychiatric patients (non-psychotic and non-medicated) compared with Red Cross blood donors demonstrated that "lymphocytes from the psychiatric patients had impaired repair of damaged DNA after x-ray irradiation" (Armandola, 2002). The psychiatric patients were

divided into two groups: one presenting higher distress symptoms and one presenting lower distress symptoms. The group displaying higher distress symptoms demonstrated poorer DNA repair. "An additional study, conducted in rats, also suggested that stress may alter DNA repair mechanisms" (Armandola, 2002).

The process of apoptosis (programmed cell death) is essential in the destruction of cancer cells. Cytotoxic T lymphocytes are programmed to destroy such cells. A study on the susceptibility to growth factor deprivation-induced apoptosis and their inhibition by phorbol ester (a tumor promoter) was conducted using medical students before and during exam periods. The inhibition of apoptosis was enhanced during exam periods. Increased resistance to apoptosis could present another method for cancer to escape destruction by the body's immune system.

Many studies have been done to demonstrate the correlation between cancer and stress in animals. The problem with animal experimentation is that there are numerous variables that seem to affect cancer in animals.

Handling, overcrowding, and being intimidated by other dominant animals seem to facilitate tumor growth. The promotion of tumor growth and stress is also dependent upon the "type and

timing of the injection of tumor cells and the type of animals used in the studies" (Azar, 1999).

Although there are many theories regarding stress and the development of cancer, they have not been proven. The Type C personality, for example, may not be the cause of cancer but the result of having an upsetting disease.

People diagnosed with cancer experience dramatic emotional changes. It is extremely difficult to link behavior and psychological stress to physical changes that influence tumor progression due to the fact that patients receive treatments that can alter any or all of these factors. For example, the side effects of chemotherapy can be immunosuppression.

The stress an individual feels may not necessarily be directly manifested in the development of cancer. It is possible that stress leads to poor lifestyle choices that result in the occurrence of cancer (Goleman & Gurin, 1993). Stress, attitudes, and beliefs can affect lifestyle choices and health-related behavior. For example, an individual under stress may smoke cigarettes or drink alcohol. These behaviors have been proven to increase the risk of cancer. Other health-related behaviors have been correlated with cancer. For example, one-third of all cases of cancer can be attributed to poor diet.

Another current theory about psychological and cognitive states and cancer development suggests that certain negative emotional states (such as depression) may have evolved as part of the sickness response to conserve energy during times of infection.

There is a new theory that is challenging Hans Selye's General Adaptation Syndrome theory (GAS). Selye believed that everyone goes through the same set of hormonal and immune system changes. This new theory suggests that there are two stress reactions. One reaction is the typical fight-flight response, but the other reaction is of withdrawal. This withdrawal reaction conserves energy. These reactions have been demonstrated using animals.

Another problem with researching stress and tumor growth in humans is that researchers cannot expose humans to tumor cells as they can with animals (Azar, 1999). Researchers often have to interview people with cancer in regards to their stress levels before their diagnosis. The interview style of data collection could lead to inaccurate self-report. A person who is now living with cancer and its treatments may look back at their life before the diagnosis and think, in comparison, that it was much more stress free.

A large longitudinal study is necessary to ultimately establish the correlation between psychological stress and carcinogenesis. A reliable study should include a sufficient number of healthy participants. The study should monitor them for about twenty years. A psychological assessment should be done periodically throughout the twenty-year span. The psychological assessment would determine the stress levels of the individuals throughout the study. This type of longitudinal study will allow researchers to see who develops cancer, who will survive it, and who will not develop cancer over time.

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References

- Armandola, E.A. (2002). "Psycho-oncology and cancer: sifting through the evidence". April 25, 2003, medscape.com.
- Azar, B. (1999). Probing links between stress, cancer. *APA Monitor*, 30(6).
- Benson, H., & Stuart, E.M. (1992). *The wellness book: the comprehensive guide to maintaining health and treating stress-related illness* (pp. 323-324). New York, NY: Birch Lane Press.
- DeAngelis, T. (2002). A bright future for PNI. *APA Monitor*, 33(6).
- Dacher, E.S. (1991). *PNI: Psychoneuroimmunology the new mind/body healing program* (pp. 22; 71-73). New York, NY: Paragon House.
- Diurnal, D., Sephton S.E., Sapolsky, R.M., Kraemer, H.C., & Spiegel, D. Cortisol rhythm as a predictor of breast cancer survival. (2000). *Journal of the National Cancer Institute* 92(12), 994-1000.
- Kielcot-Glaser, J.K., & Glaser (1999). Psychoneuroimmunology and cancer: fact or fiction? *European Journal of Cancer*, 35(11), 1603-1607.

Goleman, D., & Gurin, J. (Eds.). (1993). *Mind body medicine: how to use your mind for better health* (pp. 87-88). Yonkers, NY: A Division of Consumers Union.

Martin, P. (1997). *The healing mind: the vital links between brain and behavior, immunity and disease* (pp. 228-229). New York, NY: St. Martin's Press.

Pearsall, P. (1987). *Superimmunity: master your emotions & improve your health* (pp. 103-105). New York, NY: Mc-Graw-Hill Book Company.