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PERPLEXING IMMUNE RESPONSES TO STRESS

KEYWORDS: "Fight or flight" responses, Alarm Reaction, stress and tuberculosis, MHC, rheumatoid arthritis, systemic lupus, Hashimoto's disease, multiple sclerosis, Graves' disease, *Kreigbasedow*, *Schreckbasedow*, natural killer, helper and suppressor cells, TNF, IL, IFN, TGF, psychoneuroimmunology, psychoelectroneuroimmunology

Consumers are increasingly barraged by advertisements for supplements and services that promise to improve immune system function. Protection is allegedly provided against everything from the common cold and baldness to cancer and AIDS. How these and many other benefits are achieved is not explained, although some state they boost immune system responses suppressed due to stress. This is reminiscent of similar misleading promotions that have brought in millions for weight loss products that also allegedly work by reducing stress. While supplement manufacturers are not required to prove any claims, such statements are seemingly supported by citing totally irrelevant scientific studies showing that stress can suppress immune defenses as well as cause weight gain and abdominal obesity.

The immune system provides a barrier that prevents microorganisms from invading the body. If this initial line of defense is breached, a cascade of chemicals are activated that can rapidly identify and destroy the invader.

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However, the immune system can also be a two-edged sword. Reactions to pollens, mold and other allergens produce itchy eyes, runny noses, sneezing, wheezing, skin rashes or hives. When severe, they can cause sudden death due to anaphylactic shock in certain patients who have become sensitized to penicillin, aspirin or even a bee sting.

Boosting the immune system's response in such situations might do much more harm than good. If this seems confusing, consider the following. With respect to the immune system's ability to prevent cancer, the two most common cancer treatment modalities are radiation and chemotherapy. **However, both of these can also cause cancer.** Patients and others who are exposed to large amounts of radiation have a significantly increased incidence of thyroid and other cancers decades later. This effect is cumulative and is also seen in patients subjected to excess amounts of radiation from repeated x-rays, and other diagnostic imaging procedures. Chemotherapy, which is one of the most effective treatments for many malignancies, usually involves prescribing **drugs that suppress the immune system.** Anti cancer medications, which are the second most frequently prescribed, brought in almost \$18 billion in 2007. These same drugs are also routinely used to prevent rejection of transplanted hearts, kidneys and other organs or tissues. Unfortunately, recipients are similarly at significantly increased risk of subsequently developing malignancies like non-Hodgkins lymphoma and skin cancers, often within a few years.

Immune system responses to stress are also complicated and confusing. Severe, short-term stress tends to bolster immune defenses to provide prompt protection, whereas chronic, sustained stress has the opposite effect. And both brief and protracted stress can trick the immune system into perceiving that healthy normal tissues are foreign invaders that must be destroyed. This deviant response is dangerous and can contribute to the development of multiple sclerosis, lupus, rheumatoid arthritis, pernicious anemia, diabetes, thyroid disorders and numerous other autoimmune diseases, depending on which systems, organs and tissues are targeted.

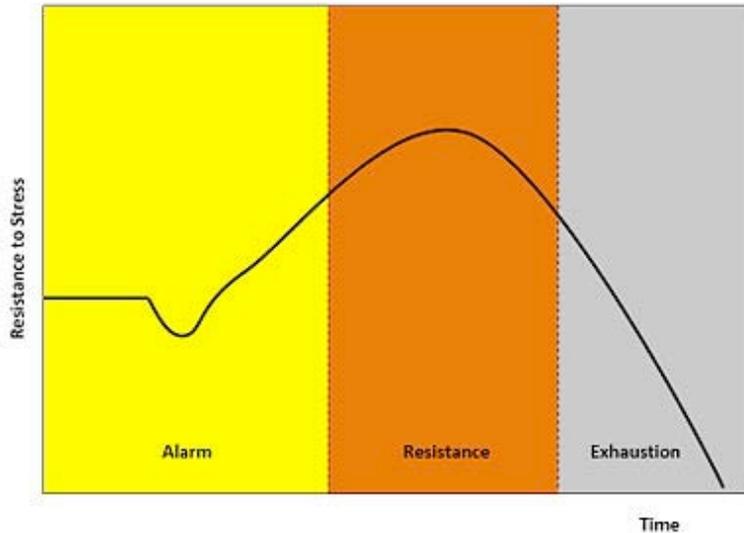
Stress, The General Adaptation Syndrome And Diseases Of Adaptation

These observations are consistent with Hans Selye's General Adaptation Syndrome and his concept of "Diseases of Adaptation" due to stress. Selye, who coined the term stress as it is presently used, did many thousands of studies on experimental animals that he subjected to severe stress. Some of these were so cruel that they would never be permitted today, including: sewing their eyelids back and shining very bright lights in their eyes for hours, subjecting them to deafening noise, forcing them to constantly swim vigorously in an inescapable container to prevent drowning, exposure to extremes in temperature ranging from freezing to being placed in boiling water, and causing severe psychological frustration due to an inability to avoid a potentially lethal threat that never materialized.

Selye was surprised to find that, regardless of the nature of these very different stressors, all his animals exhibited the same three identical pathologic findings at autopsy: atrophy of the thymus and lymphatic tissues,

enlargement of the adrenals, and multiple small ulcerations in the stomach. There could be specific lesions, such as burns or frostbite in the skin, and damage in other tissues, depending on the nature of the stressor, but every animal showed this same triad of nonspecific stress effects.

The General Adaptation Syndrome



Selye called this initial response the "Alarm Reaction", and viewed it as a "call to arms" of the body's defenses. Further exposure to the stressor resulted in a "Stage of Resistance" in which the body's defense mechanisms were mobilized to provide maximum resistance to the threat. If subjection to the stressor persisted, a "Stage of Exhaustion" followed, in which all the body's resources were depleted, and the inability to maintain normal function eventually resulted in death. He termed these three sequential phases "The General Adaptation Syndrome."

The "Alarm Reaction" triad of pathology occurred within 6 to 36 hours, depending on the severity and nature of the stressor, and consisted of a shock and subsequent counter shock component. The initial "fight or flight" response, that had been described decades previously by Walter Cannon, was characterized by marked stimulation of the sympathetic nervous system and an outpouring of adrenaline from the adrenal core, or medulla. Myriad responses were automatically activated throughout the body that had been exquisitely developed and refined over the lengthy course of evolution to preserve life. Quicker blood clotting minimized excess loss from laceration or internal hemorrhage, blood flow was shunted away from the stomach and gut, where it was not immediately needed for digestive purposes, to the large muscles of the extremities to increase tension that provided greater strength in combat or speed of flight away from a scene of potential peril. A rise in heart rate and blood pressure furnished more oxygen and nutrients to the brain to improve decision-making, pupillary dilation increased the range of vision, and numerous other responses were initiated that were **designed to help our primitive ancestors cope with some physical threat.**

Selye extended Cannon's research by demonstrating the crucial role of pituitary stimulation of the adrenal during stress. This resulted in an increased secretion from the adrenal cortex (outer shell) of glucocorticoid hormones like cortisone and cortisol. These augmented the rise in blood sugar and blood pressure seen during "fight or flight" and increased the

production of stomach acid. More importantly, adrenocortical hormones had powerful anti-inflammatory effects that helped to explain the three pathologic changes he had consistently observed. Adrenal enlargement was due to hypertrophy of the cortex, where cortisol is manufactured, and the stomach ulcerations resulted from increased acid secretion and suppression of protective inflammatory responses. Why there was atrophy of the thymus and lymph glands was less clear, since little was known about how the immune system functioned at the time. It was subsequently found that B lymphocytes were largely responsible for immediate humoral responses like allergic reactions, that delayed cell-mediated immune responses were governed by specialized T (for thymus) cells, and that cortisol had powerful immunosuppressant effects that affected both of these responses.

However, the nature of stress today is no longer an occasional encounter with a saber-toothed tiger, warring tribe or natural disaster. Contemporary stress is much more apt to stem from emotional challenges that often occur several times a day, like confrontations with customers, coworkers and family, or being stuck in traffic for an hour or more on the way to an important flight. Unfortunately, our bodies still automatically respond with those same archaic "fight or flight" responses that are no longer purposeful, but prove harmful. Repeatedly invoked, it is easy to see how they could contribute to heart attacks, hypertension, stroke, ulcers, muscle spasm, low back pain, diabetes and other diseases of civilization. Autopsy studies conducted during the later stages of the General Adaptation Syndrome revealed microscopic changes in the kidneys, cardiovascular system, GI tract, soft tissues and other structures that were almost indistinguishable from pathology seen in patients with heart attacks, stroke, ulcers, rheumatoid arthritis and other connective tissue diseases. Selye reasoned that if stress caused such lesions in animals, perhaps it also contributed to their human counterparts, and referred to them as "Diseases of Adaptation".

Selye's concept of "Diseases of Adaptation" attracted widespread interest because it was counter to contemporary thinking. Due largely to the research of Louis Pasteur, Robert Koch, and Koch's Postulates, physicians had been taught that each disease had its own, very specific cause. Tuberculosis was caused only by the tubercle bacillus, and anthrax, cholera, syphilis and other infectious diseases were similarly due to different microorganisms. The clinical manifestations of tuberculosis or syphilis could vary considerably, depending on which organs or structures were affected, but it was still the same disease. Stress and other factors could increase the likelihood of infection, and it had been previously believed that tuberculosis was caused by poor personal hygiene and close, unsanitary living conditions. It was also possible to be infected with the tubercle bacillus and have no signs or symptoms. Nevertheless, clinical tuberculosis could not occur

unless the tubercle bacillus was present. Anecdotal reports emphasized the ability of emotional distress to activate a quiescent infection or accelerate its progress. This was vividly illustrated by operatic heroines like Violetta in *La Traviata* and Mimi in *La Boheme*, who steadily wasted away and eventually succumbed to tuberculosis due to their tragic love affairs.

Both Cannon and Selye were strongly influenced by the research of the great 19th century physiologist Claude Bernard, who emphasized that good health and life itself depended entirely on maintaining the stability of the internal environment whenever it was challenged. Walter Cannon called this homeostasis. From Bernard's perspective, clinical disease resulted not as much from microbial invaders to which we are exposed daily, but rather **how the body responded** to these and other challenges. Bernard engaged in frequent debates with his colleague, Louis Pasteur, at the prestigious *Académie Française*, where they sat next to one another. Pasteur, who was the prime proponent of the germ theory of disease, allegedly admitted on his deathbed, "*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.**) Astute physicians also recognized the role of stress. Sir William Osler, who wrote, "It is much more important to know what sort of patient has a disease than what sort of disease a patient has", told his students that **the outcome of tuberculosis depends more on what goes on in the head than the chest**. When cortisone became available to treat rheumatoid arthritis a half century later, it soon became apparent that long term use resulted in a recurrence of previously quiescent tuberculosis due to suppression of normal immune system defense mechanisms.

And just as each infectious disease had its own specific cause, other diseases were also due to a deficiency in some single nutrient. Scurvy was caused only by lack of vitamin C. Rickets resulted only in children with insufficient vitamin D intake or exposure to sunlight. The same was true for beri-beri and other vitamin deficiency disorders. Each disease was believed to have its own specific cause. What Selye proposed was exactly the opposite, namely that his "Diseases of Adaptation" could have many different causes. He frequently complained to me that "Diseases of Maladaptation" to stress might have been a much more appropriate description.

Are Autoimmune Diseases Also Due To Maladaptive Responses To Stress?

Similarly, it appears that very different stressors can also cause or contribute to the same autoimmune disease by damaging the immune system's ability to recognize normal healthy tissue. The immune system consists of a complex network of organs and cells that includes: bone marrow, white cells, the thymus, lymphoid tissue in the throat (tonsils) and gut (Peyer's patches) as well as the spleen. These all work in concert to

protect and defend the body from infections, pollens and other allergens or toxins. Autoimmune diseases result from a failure of this integrated effort, and normal tissue is attacked because it is perceived as a foreign invader rather than as part of the body. A properly functioning immune system recognizes healthy normal tissue because the membrane of every cell in our bodies is studded with the same specific proteins in identical configurations that are referred to as its MHC (major histocompatibility complex). The MHC provides a pass code that tells the immune system to ignore them. Since pollens and bacteria do not possess this identical MHC shield, the immune system activates responses to destroy these intruders.

Each of us has our own unique or nearly unique MHC, which poses a problem with respect to transplantation of organs and tissues. As a result, transplant donors tend to be close relatives that are most likely to have genetically similar MHC's, or others with very close matches for the major histocompatibility antigens. But even in such situations, it is necessary to perpetually take immunosuppressant drugs to prevent rejection of transplanted tissues and organs by recipients. This can result not only in increased risk of subsequent cancers, but also greater susceptibility to infections. In addition, these drugs can have serious side effects, such as increased bleeding, interactions or interference with other medications, and could prove dangerous for patients with kidney or liver disease. Immunosuppressant drugs are also used to treat autoimmune diseases that result when the immune system fails to recognize the protective MHC patterns on cell walls of healthy tissues and attempts to destroy them.

There are over 100 known or suspected autoimmune diseases. Some can involve multiple sites around the body, especially the joints, as in rheumatoid arthritis. Systemic lupus erythematosus may also affect the skin, kidneys, heart, lungs and red blood cells. Other autoimmune diseases target one specific organ, such as the thyroid, but in ways that have very different widespread systemic repercussions. Hashimoto's thyroiditis causes hypothyroidism and can also lead to Hashimoto's encephalopathy, a central nervous system disorder that often progresses to dementia. Graves' disease is a common cause of hyperthyroidism that is associated with diffuse goiter and exophthalmos (bulging eyes). But both increased and decreased thyroid function due to these autoimmune diseases affect the cardiovascular system, nervous system and muscular system to produce a variety of very different signs and symptoms in sites and structures all over the body.

Autoimmune diseases result from a combination of inherited and environmental factors. Individuals with a family history or specific genes are particularly susceptible when they are exposed to certain environmental triggers, as well as nonspecific stressors. High dietary iodine intake is known

to trigger autoimmune thyroid disease, and exposure to silica has been implicated in scleroderma. Symptoms and signs in autoimmune diseases like multiple sclerosis often wax and wane, sometimes disappearing completely for many years before they return with a vengeance. Graves' disease may be self-limiting and resolve spontaneously after running its course. Other autoimmune diseases, like systemic lupus erythematosus, tend to progress, especially in young patients, where it is more likely to prove fatal. The ability of stress to precipitate the onset or recurrence of these and other autoimmune diseases has long been recognized. Studies also suggest that stress can aggravate or accelerate the downhill course of almost every autoimmune disease. Over 100 years ago, Osler emphasized a variety of behavioral disturbances due to emotional stress that appeared to be associated with the development of a syndrome that was subsequently determined to be systemic lupus erythematosus.

The relationship between stress and multiple sclerosis was emphasized by the French pathologist Jean-Martin Charcot in his initial 1868 description of the disease. He had been particularly interested in hysteria, which was characterized by bizarre emotional and behavioral symptoms that frequently followed some severely stressful event. However, in some patients, it progressed to a disease called "creeping paralysis" characterized by a triad of nystagmus, slurred speech and an intention tremor that could be either intermittent or progressive and even fatal. At autopsy, Charcot found "*la sclerose en plaques*" (multiple sclerosis) involving the optic nerves, cerebellum, brain stem and spinal cord that explained these three neurological signs. The onset of multiple sclerosis (MS) is usually between the age of 20 and 40, it is 50% more common in women than men, and more likely to occur in Caucasians of Northern European ancestry. The incidence rises as you move away from the equator and can be five times higher in North America and Europe compared to the tropics. There are also genetic influences, since there is often a family history. In addition, MS is not seen in Eskimos, gypsies or Bantus, and is rare in native North and South America Indians, Japanese and most Asians.

Multiple sclerosis may be precipitated by viral infections and vaccines that target the nervous system and elicit immune responses that damage the protective myelin sheath around nerves. Human herpesvirus 6 (HHV-6) was found in brain tissue genetic material as well as the spinal fluid and lymph nodes in three out of four patients in one study. In another, 73% of patients with chronic MS had an increased antibody response to HHV-6 antigen compared to only 18% of matched controls. About one third of these MS patients had active herpes virus in their blood compared to none in any of the controls. HHV-6 infection in experimental animals has been shown to erode the myelin sheath, so there is good reason to suspect its ability to

cause multiple sclerosis in humans. Further support comes from studies of fresh MS lesions that show macrophages, plasma cells, T-lymphocytes and other immune system components. It is estimated that nine out of ten Americans harbor the HHV-6 virus. The vast majority have no related symptoms until immune defense mechanisms are suppressed by stress and the virus is activated. This is frequently seen with the herpes simplex virus, which lies dormant, but erupts in recurrent cold sores on the face, lips or genitalia when triggered by emotional stress, menstruation, or an infection that causes "fever blisters".

It is not surprising, therefore, that in his initial report on multiple sclerosis, Charcot noted that stress, and particularly the trauma of grief, seemed to precipitate the disease. However, a 22-year-old Englishman, Augustus Frederick d'Este, a cousin of Queen Victoria, may have been the first to describe this almost a half century earlier. On December 13, 1822, he experienced the sudden onset of a severe disturbance in vision shortly after attending the unexpected funeral of a relative and very close friend. As he wrote in his diary, "I was obliged to have my letters read to me, and their answers written for me, as my eyes were so attacked, that when fixed on minute objects, indistinctness of vision was the consequence. Soon after, they completely discovered their strength and distinctness of vision." Although he made an initial recovery, subsequent diary entries leave little doubt that this was the onset of MS, which later progressed. Temporary blindness due to inflammation of the optic nerve is seen in over half of MS patients and is frequently the first sign.

Several studies have reported that a significant number of MS patients report having suffered a relapse or worsening of their symptoms during or shortly after some severe stress. Others have conflicting results and one study found no difference in the incidence of life change event stress scores in the month prior to a relapse, compared to baseline levels. However, when the same patients were interviewed two years later, 60% believed that stress had adversely affected their condition and almost half felt that stress had been responsible for a relapse. This is supported by Mount Zion Multiple Sclerosis Center researchers in San Francisco who followed 50 middle-aged patients with intermittent or progressive MS. All were rated monthly for levels of stress, anxiety and depression, as well as clinical status, and brain lesions were measured based on sophisticated MRI scans. There was a clear correlation between increased brain lesions and stress levels as assessed by both major life change events and daily Hassle scores. There was also an association between depression and new brain lesions but this was not as statistically significant. However, since depression and grief have also been shown to suppress the immune system, it is not surprising that they are often associated with a worsening of MS and other autoimmune diseases.

Graves' Disease was also generally acknowledged to be due to "prolonged worry and sudden shock" during the nineteenth century. Although other cases of exophthalmic goiter were recognized before the 1800's, the first accepted report was made by Caleb Parry, a physician and farmer from Bath, England. In 1786, he described a patient who developed severe palpitations and diffuse goiter shortly after giving birth. Postpartum stress and depression are not uncommon and this period is now recognized as a risk factor for thyroid and other autoimmune diseases. Parry's second patient developed similar symptoms and exophthalmos following a severe shock. However, these and six additional case reports on other diseases were not published until 1825, three years after his death. Robert Graves, an Irish physician, who was unaware of Parry, published a report in 1835 of three women with goiter and palpitations. His first case occurred in a young woman two weeks after having been thrown from a carriage. Karl von Basedow, a German physician who independently described several other cases in 1840, also emphasized the important role of stress. (In Europe, exophthalmic goiter is known as Basedow's disease or Graves-Basedow disease, although Osler and others felt this honor belonged to Parry.)

An increased incidence of Graves' disease has been documented during every war since the Franco-Prussian. The German term *Kriegsbasedow* reflects this and the French refer to the thyroid as "*la glande d'emotion*". During the 1939-1945 war, hospital admissions for Graves' disease in occupied Scandinavia increased at least five-fold, and quickly fell to normal following liberation. Although there is no animal model, it has been observed that in some strains of wild rabbits, the fear induced by fierce canine or human pursuit can cause the very rapid development of "stress thyrotoxicosis", with exophthalmos and microscopic changes consistent with overactivity of the thyroid. A sudden fright in humans can also cause acute exophthalmus and thyroid enlargement with pulsating thrills in a matter of hours, a condition called *Schreckbasedow*.

Numerous clinical reports confirm not only the causative role of stress in Graves' disease but also its remission when stress disappears. In 1917, a bride of only 6 months was told that her husband had died at sea after his ship had been torpedoed. Within three months, she developed typical exophthalmic thyrotoxicosis that failed to respond to sedatives and she was confined to bed rest in a darkened room to promote her recovery. Her husband, who had survived the torpedo attack, subsequently returned and her goiter and bulging eyes rapidly vanished with no further treatment. Her complete remission lasted for 46 years until she was 63, and was with her husband in their kitchen when he suddenly dropped dead due to a massive heart attack. Her thyrotoxic goiter again returned within three months.

Another report involved sisters who had asymptomatic goiters for several years. In 1923, the older sister developed thyrotoxicosis requiring surgery and died on the operating room table. The younger one, who was 18, thought that her sister would have died anyway "from the tumor in her throat" and feared for her own life. Over the next six months she became thyrotoxic and was successfully treated by surgery. She remained symptom free for 36 years when she detected a lump in her right breast and was certain it was cancer. Although it was found to be benign, her exophthalmic thyrotoxicosis recurred within six months.

Stress has also been frequently implicated in triggering other autoimmune diseases, especially those that tend to have a family history, like psoriasis, pernicious anemia, diabetes and alopecia areata. While genetic links are less common in biliary cirrhosis and interstitial cystitis, stress can worsen these and other autoimmune diseases because of cortisol's detrimental effects on lymphoid tissues and white blood cell production, as initially observed by Selye. In the early days of stress research, when accurate steroid measurements were not available, stress levels were assessed based on their ability to lower lymphocytes and eosinophils, another white blood cell that is elevated during allergic reactions. Cortisol normally keeps the immune system in check to prevent excessive and uncontrollable inflammatory responses. Autoimmune diseases may result due to disturbances in the hypothalamic and pituitary hormones that stimulate cortisol production, so that inflammation continues even when it is no longer needed and is harmful. Alternatively, because of abnormalities in its cortisol receptors, the immune system may not respond as well to cortisol's anti-inflammatory effects. This could explain why cortisol and more powerful similar synthetic steroids are so effective in inflammatory autoimmune diseases like rheumatoid arthritis. Conversely, chronic stress, produces elevated levels of cortisol that dampen defensive immune responses. As a result, Alzheimer caregivers who work long hours for many months are more prone to severe infections, are much less likely to respond to vaccines by producing protective antibodies, and have delayed wound healing.

It seems curious that cortisol is so effective in treating allergies, but as confirmed in a recent report, stress, which increases cortisol, makes hay fever worse and last longer. A similar paradox is seen in rheumatoid arthritis. Little was known about the mechanisms mediating these complex interrelationships until a half century ago, when specific immune system components involved in various responses started to be identified. Interest in the influence of stress on the immune system accelerated with George Solomon's psychoimmunology research and subsequently skyrocketed, after Bob Ader established psychoneuroimmunology as a distinct discipline. His textbook, *Psychoneuroimmunology*, published in 1981, contained 17

chapters that gave a name and identity to diverse attempts to understand how brain and immune system bidirectional interactions could affect health. Some idea of the explosive growth in this field is that the third edition, published in 2001, consisted of 67 chapters that filled two very thick volumes. Since then, thousands of papers on various aspects of this topic have appeared annually in scientific publications and there are journals devoted to psychoneuroimmunology, neuropsychopharmacology, etc.

What And Where Is The Immune System And How Can It Be "Measured"?

Like stress, psychoneuroimmunology rapidly moved out of the realm of researchers into the public domain and became a popular buzz word. Entrepreneurs and self-appointed psychoneuroimmunology and "wholistic" practitioners made extravagant claims about the ability of the mind to cure cancer and other deadly diseases. Products were promoted that presumably facilitated this by boosting natural antioxidants or supplements that duplicated their ability to block free radicals. Few physicians or patients appreciated that there were various types of free radicals, that antioxidants had different actions, or that taking megadoses of antioxidants like vitamin C to boost immune resistance, as advocated by Linus Pauling, could backfire. Indeed, when taken with iron, another popular supplement, vitamin C actually promotes oxidation. More importantly, this outpouring of scientific articles failed to reveal anything useful for treating patients and usually generated more questions than answers about immune system function.

Nevertheless, in these and other publications, the "immune system" was often described with an air of authority as being "suppressed", "depressed", "stimulated", "enhanced", "compromised", "disturbed", "deranged", etc. But what do these adjectives actually mean? As emphasized, "the immune system", consists of a complex network of organs, glands, tissues, specific cells and cell products like antibodies. Each of these can be "measured" by different criteria but what is their clinical significance? Some, such as natural killer, helper, and suppressor cells, whose names suggest specific functions, may provide information about the status of some diseases but not others. The same holds true for assessment of cytokines like interleukins (IL), interferons (IFN) tumor necrosis factors (TNF) and transforming growth factors (TGF). Other immune system components are identified by a very complicated and confusing alphabet soup of letters, numbers and symbols with presumed prognostic potential. For example, some of those used to assess the status of HIV infection and AIDS include CD4+, CD4+/CD8+ ratio, NK-associated CD 16+ (leu11), leu7-and CD 16+(leu11), leu7+ lymphocyte subsets, the CD45RA+CD4+ subset that activates suppressor/cytotoxic (CD8+) cells, CD26, IL-2, IL-12, and IFN- γ .

Immune responses to stress can be evaluated by relatively cruder techniques, such as macrophage activity by chemiluminescence and changes in complement C3, opsonins or properdin. More recent research is based on test tube studies of the effect of mitogens like phytohemagglutinin (PHA) and concanavalin A (ConA) on T cells. However, it is not clear whether these mirror what happens in the body. In addition, we may all respond to the same stressor in very different ways. Depending on which immune system component is measured, **the same study could conclude that immune function was increased, lowered or not affected.**

"To measure is to know", and as the great 19th century physicist Lord Kelvin added, **"If you can't measure it, you can't improve it." But you can't measure anything until you are able to define it.** Scientists have long complained that finding a satisfactory definition of stress that all can agree on is like trying to nail a piece of jelly to a tree. This also applies to the immune system. Manifestations of stress like anxiety, anger and depression are easier to define and can be measured by relevant nervous system and endocrine responses. People can tell you how angry or depressed they feel but not how well their immune systems are functioning. And there are so many different immune system measures, it is difficult to be certain which ones would be particularly pertinent for any given patient.

Unlike endocrine and nervous system responses to stress, there are humoral as well as hardwired connections between the brain and immune system that may be involved. Immune function can also be significantly influenced by electromagnetic fields from external sources like high power lines, cell phones and appliances. Moreover, there are similar energies generated internally that might provide answers to puzzling questions such as immune responses to placebos and spontaneous remission of cancer in patients with a very strong faith. There is growing evidence of communication in the body via a closed electrical circulatory system, and, as I have previously proposed, psychoelectroneuroimmunology may emerge as a new discipline.* In the interim, be cautious about conclusions dealing with the effects of "stress" on "the immune system" — and stay tuned for more about this!

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*Rosch, P.J. Future Directions In Psychoneuroimmunology: Psychoelectroneuroimmunology? In Leonard BE, Miller K. (eds) *Stress, the Immune System and Psychiatry*, 1995; John Wiley and Sons, London.

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