REVIEW ARTICLES

The Influence of the Psyche and the Brain on Immunity and Disease Susceptibility: A Critical Review

MALCOLM P. ROGERS, MD, DEVENDRA DUBEY, PHD, AND PETER REICH, MD

In critically reviewing the sources of evidence connecting psyche and brain with the immune system, the authors include a brief review of current knowledge of the immune system, its interactions with the neuroendocrine system, and other factors influencing its regulation. These include developmental stages, aging, rhythmicity, and a variety of exogenous influences. The need for developing further information about normal base lines is emphasized. Against that background, many sources of data demonstrating connections between the central nervous system and the immune system are presented: indirect evidence from clinical and experimental illnesses involving the immune system, and direct changes in either humoral or cellular immunity after natural or experimental stress, conditioning, hypnosis, and direct brain stimulation. Possible mechanisms are discussed, as well as some important methodological issues for further research.

INTRODUCTION

Historically, psychosomatic medicine has often followed advances on the somatic side of the mind-body axis. For example, developments in endocrinology, cardiovascular and renal physiology, and neurophysiology have each been associated with surges of research on the relationship between mental states and disorders and normal functions of these specific areas. As new biological techniques and approaches emerge, they become the instruments of investigators who are trying to narrow the gap in the psychosomatic process referred to by Weiner as "the transduction of experience" (1).

In recent years one of the most rapidly advancing areas in medicine has been immunology and, not surprisingly, its interactions with various psychological states, especially those associated with stress, have been the focus of intense interest. Two reviews, one by Amkraut and Solomon (2) and the other by Stein and colleagues (3), have summarized much of the recent research in this area. A central premise underlying much of the work that has been done is that stress may increase an organism's vulnerability to certain diseases by means of exerting an immunosuppressive effect, especially those diseases intimately associated with immunologic mechanisms, such as infection, malignancy, and autoimmune disease. The purpose of this article is to re-

From the Division of Psychiatry, Department of Medicine, Peter Bent Brigham Hospital, the Department of Psychiatry, Harvard Medical School, and the Sidney Farber Cancer Institute, Boston, Massachusetts.

Address reprint requests to: Malcolm P. Rogers, M.D., 721 Huntington Avenue, Boston, MA 02115.

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view in a critical fashion the evidence for this premise, including several areas not covered in recent reviews and some which have developed since their publication. In doing so, we will also briefly review recent advances in our knowledge of the immune system, and the many factors which either endogenously or exogenously influence its regulation. The investigation of psychosomatic relationships involving the immune system offers us a unique opportunity. The immune system has a fundamental role in the maintenance of body homeostasis and health (4). Even minor fluctuations in this system have direct implications for the development of disease. In recent years there have been many advances in our understanding of the effect of mental states on the endocrine and autonomic nervous systems, although the implications of those changes for disease susceptibility have often been less obvious. The immune system provides us with a further critical link in the psychosomatic process and disease susceptibility.

IMMUNOLOGY: BRIEF REVIEW INCLUDING RECENT ADVANCES

The field of immunology is expanding at an extraordinarily rapid pace. Accordingly, our knowledge of the normal regulation of immunity and the choices of measurable immune functions which might provide the most sensitive index of immunocompetence are also changing. Before focusing on more recent advances, a brief overview of the entire system might be helpful. For additional reading, we refer the reader either to Austen's "Introduction to Clinical Immunology," in Harrison's *Principles of Internal Medicine* (5), or to Roitt's *Essential Immunology* (6).

The immunologic apparatus is broadly divided into two large components. The first is that of *humoral, or antibody-mediated reactions*. In these, antigen-specific reactions are carried out by various classes of immunoglobulin molecules, such as IgA, IgG, IgM, or IgE. When stimulated by specific antigens, *B lymphocytes* are transformed into plasma cells, actively producing a specific antibody. These antigen-antibody interactions are closely associated with amplification systems involved in the inflammatory process, such as the classical or alternate complement pathways. Such reactions include defenses against toxic and bacterial antigens, transfusion reactions, and various forms of autoimmune reactions (hemolytic anemia).

The second major component is that of *cell-mediated immunity*, the primary process involved in delayed hypersensitivity (such as the tuberculin skin test) and the rejection of transplanted tissue. In this system, *T lymphocytes* are activated by specific antigens interacting with surface receptors and release nonantibody substances called lymphokines. These in turn act upon other cells which result in an inflammatory process. Neither circulating antibodies nor the complement system are involved in cell-mediated immunity.

An individual's immune system has the capacity to differentiate between self (to which there is *tolerance*) or foreign macromolecules (to which an immune response is directed). When an antigen is first introduced, it triggers a *primary* humoral or antibody response. After a period of time, the level of antibody declines but after reexposure to the antigen (for example as with a booster shot) an enhanced *secondary* response is elicited. In general, an antigen is taken up by a

macrophage in the spleen if administered intravenously, or in the lymph node if administered subcutaneously. The macrophage in turn presents the antigen to the lymphocyte for recognition. Lymphocytes are thought to be genetically preconditioned to interact with a particular antigen. It is the B lymphocyte, derived from bone marrow stem cells in mammals, which produces immunoglobulins when so stimulated. The B lymphocytes represent about 20% of the peripheral blood lymphocytes and about 50% of the spleen lymphocytes.

IgG composes 70–80% of the serum antibodies in the human being and is almost exclusively responsible for the antibodies to viruses, toxins, and gram-positive pyogenic bacteria. *IgM* makes up between 5 and 10% of the total serum antibody, typically elicited by antigens of gram-negative bacteria. *IgA* comprises about 10–20% of the total serum antibody and functions predominantly in body secretions, for example, in parotid saliva, nasal, and gastrointestinal secretions. By activating mast cells in the presence of specific antigens, *IgE* plays an important role in immediate hypersensitivity (allergic) reactions, such as in anaphylaxis. The level of humoral immunity can be assessed by measurements of serum immunoglobulin levels, by specific antibody titers raised to specific antigens, or, in fact, by measuring the activity of plasma cells in the spleen after antigenic stimulation (the so-called plaque-forming assay). It is also possible in vitro to stimulate B lymphocytes differentially and to measure various functional capacities of these cells alone.

One of the most important advances in recent years has been the differentiation of B lymphocytes from T lymphocytes. The thymus gland has a critical role in the differentiation of T lymphocytes from precursor cells and has other important regulatory functions, especially in cellular immunity. T lymphocytes, those derived from the thymus, make up about 80% of peripheral blood lymphocytes. As mentioned above, they are involved in cell-mediated immunity, such as delayed hypersensitivity reactions and transplant rejection reactions. The differentiation of T and B lymphocytes has led to a proliferation of different tests which provide indices of cellular immunocompetence. In addition to the older in vivo methods, i.e., skin testing (delayed hypersensitivity to antigens such as mumps, streptokinase, or streptodornase—antigens to which virtually everyone has been exposed) and the pattern of rejection of tissue transplants (which provide only crudely quantifiable measures of T-cell function), a variety of new in vitro techniques have been developed. These include lymphocyte response to mitogens, substances like phytohemagglutinin or concanavalin A, which stimulate mitosis in these cells, T-lymphocyte cytotoxicity (the capacity of T cells to kill cultured cells to which they have been sensitized), or the even more recent natural killer-cell activity (first identified in 1974). The latter has recently emerged as an important index of general immunocompetence because it measures a natural function of the cells without requirement of prior sensitization, and it is thought to provide an important host defense against the development of malignancy and viral infection (7). For some time the immune system has been thought to perform a surveillance function in recognizing cells undergoing malignant transformation and eliminating them before tumor growth occurs.

To make matters more complicated, it turns out that another function of T cells

is in regulating the humoral responses of B lymphocytes, either in augmenting (helper T cells) or in suppressing (suppressor T cells) such reactions. Natural killer cells have been described as another subset of lymphocytes and undoubtedly others will be defined in the future. All of these cells function in a complex, interregulatory network maintaining physiological homeostasis. The explosion of research in immunology, particularly in cellular immunology, is at the forefront of research in cancer, arthritis, transplantation, and many other medical areas, and it has opened up new vistas for the psychosomaticist. It should be obvious, however, that the immune system is a very complex network, and that there is no single measure of immunity, but many different measures. That makes a concept like immunosuppression, for example, more complicated, in that the suppression of suppressor T cells may, in fact, augment other components of the immune system, and the suppressor T cells are thought to be particularly sensitive to regulatory substances.

NORMAL REGULATION OF THE IMMUNE SYSTEM

As a Function of Time

Although we will present some intriguing data suggesting alterations in immunity after psychological stress and other central nervous system effects, our relatively limited knowledge of the normal regulation and base line of the immune system over time requires caution in evaluating the significance of many of these findings. A great variety of either congenital or acquired immunodeficiency syndromes, like the DiGeorge syndrome or an isolated deficiency of IgA, have been described and more are being described all the time. But, beyond these gross deficiencies which have obvious clinical manifestations, the question arises as to how much variability exists within individuals over time, or between racial groups, sexes, and perhaps along other dimensions. How much fluctuation is there in both cellular and humoral immune mechanisms? And, if there are differences, are they significant either statistically or biologically? For any given individual, how much variation occurs within the course of a day? A week? A month? A lifetime?

Age is certainly an important variable. It has been known for some time that in human beings humoral immunity is not fully developed at birth and does not become so until approximately 1–2 years of age. At least that is when IgM reaches adult levels. By that time IgG will also be at adult levels, but levels of IgA continue to increase throughout life (8). There is relatively little information about cellular immunity in newborns, except that it is grossly intact, as judged by the presence of delayed hypersensitivity reactions. It is unclear whether any alteration in immunologic competence occurs at the time of puberty (when the thymus gland undergoes involution), but *pregnancy* is associated with an impairment in cell-mediated immunity both in women (9) and in animals (10), presumably in protection of the fetus. Whether other major endocrinologic milestones, such as menopause, are associated with alterations in immune functions is not as yet known.

However, later stages of aging in relation to immunity is one area where considerably more data are available. Numerous changes in the immune system are as-

sociated with aging and are well summarized in a recent book (11). In brief, these include a diminution in both cellular and humoral immunity, and an increase in substances like amyloid (now identified as a fragment of immunoglobulin molecules) and autoantibodies, both of which reflect a failure in the regulation of immunity.

Do these changes associated with aging have any significance? There is evidence to suggest that they do. Increasing numbers of autoantibodies coincide with the rising risk of developing autoimmune disorders in an older population. Furthermore, the prevalence of malignancy increases in an older population and many people feel that disordered immunity contributes to the development of malignancies. There has also been more direct evidence. A prospective study of 52 persons over age 80 showed significant correlations between diminished delayed type hypersensitivity and greater mortality (12). These data lend support to the notion that immunosuppression of the magnitude that stress can induce may add to an organism's susceptibility to disease and death.

However, between the extremes of early development and old age and major life changes associated with endocrinologic shifts, we have considerably less information about the variabilities in the *normal base line*. The studies that do exist report that *human immunoglobulin levels* vary relatively widely between individuals but probably by no more than about 20% *within* individuals during the course of a year (13). Differences in sex (females have 20% more IgM) and race (blacks have more IgG than whites) are also reported (14).

Little data about the constancy of *cellular immunity* exist, although there do appear to be sex differences and probably racial differences there as well. Basically, however, no normal quantitative base lines have been established.

How much variation is there during the course of a day? We now know that there are significant circadian rhythms in immune functioning, both in humoral and cellular functions in man and in laboratory animals, much of the work having been summarized in a recent volume entitled *Chronobiology in Allergy and Immunology* (15). Included are papers describing *circadian variations* in secretory IgA, plasma cell, and immunoglobulin level response to antigen stimulation, and quantitative levels of circulating lymphocytes as well as their response to mitogenic stimulation. Recently we have found a marked diurnal variation in natural killer activity.[1]

These data should make us cognizant of the sketchy nature of the base-line patterns of immunologic variations against which attempts have been made to measure the effects of psychological stress. It is obvious that methodologic approaches in the future need to be very precise about not only the gender of the subject, but the exact stage of the life cycle and the time of day during which measurements are taken. It may also turn out that changes in immunologic rhythms may be as or more significant than demonstrated changes in isolated levels.

The Neuroendocrine Apparatus and the Immune System

A further look at the factors which regulate the immune system leads us to consider the role of the neuroendocrine sys-

[1]Rogers, MP, Dubey D, Halberg F, Yunis E: work in progress.

tem. There are by now many well-documented interactions between immune processes and neuroendocrine functions, described in recent reviews by Besedovsky and Sorkin (16), Ahlqvist (17), and Wolstenholme and Knight (18). In all likelihood, the diurnal variations in rhythmicities in the immune system described above are intimately related to well-established rhythmicities in the neuroendocrine system, but the exact interrelationships remain to be worked out.

In any case, the neuroendocrine system appears to be essential for the normal ontogenetic development of the immune system and vice versa. Neonatal thymectomy in mice, in addition to impaired cellular immunity, leads to altered sexual maturation, adrenal hypertrophy, and other endocrine disturbances. In fact, for a long time the thymus has been assumed to be an endocrine organ, and more recently, a thymus hormone-like substance known as thymopoietin has been isolated, although its biological properties are not as yet well understood (19). The thymus in turn is dependent on a normal neuroendocrine environment, especially adrenocorticoids. Many years ago Selye described accelerated thymic involution as one of the cardinal manifestations of the stress response syndrome in conjunction with elevated corticosteroid levels and adrenal hypertrophy (20), a finding which lapsed into obscurity because the importance of the thymus in immunity was not then known. High doses of exogenous steroids are known to be immunosuppressive both in humoral and cellular immunity, and are used for this purpose in a wide range of clinical situations. It is less well known that physiological levels of corticosteroids have been found to be required for several normal functions of immunity (21). Thus, the direction of the effect of corticosteroids is dose-related. In addition to the *corticosteroids, thyroid hormone, growth hormone, insulin,* and *sex hormones* at physiological levels have all been shown to be required for the normal development and functioning of the immune system (22).

The existence of insulin receptors on the surface of lymphocytes at certain stages of activity is noteworthy in considering the interrelatedness of the immune and endocrine systems (23). In addition to this receptor, histamine, E prostaglandins, acetylcholine, and β-adrenergic catecholamines all seem to have specific receptor sites through which they affect the functional activity of lymphocytes. They all exert their effect through the second messenger system, intracellular cyclic AMP and cyclic GMP (24). The fact that cholinergic and β-adrenergic receptor sites exist on certain lymphocytes is especially relevant to our consideration of links between the central nervous system (CNS) and the immune system.

Other studies have emphasized the importance of the neuroendocrine system *during* the induction of an immune response. In one study, Besedovsky and his colleagues immunized rats with two different antigens, and then discovered a striking increase in serum hydrocortisone and a moderate decrease in thyroxine, which coincided with the time of elaboration of antibody-forming cells. That finding, associated with a simultaneous increase in electrical activity in individual neurons in the ventral medial hypothalamus of the rat, led them to postulate an *afferent pathway* between the peripheral initiation of an immune response and the hypothalamus (25). A recent report by Pierpaoli and Maestroni has suggested that pharmacologic interruption of that neuroendocrine response after immunization suppresses transplantation immune reactions. The authors made the

empiric discovery that a combination of drugs, including L-5-hydroxytryptophan (a serotonin precursor), dopamine, haloperidol, and phentolamine (an alpha adrenergic blocking agent), when administered a few days before and after immunization, led to specific and long-lasting unresponsiveness to the specific antigens administered (26).

CNS CHANGE ALTERING IMMUNITY

Having briefly reviewed the normal function and regulation of the immune system and some of the factors known to affect its homeostasis, we will now pull together evidence from various sources indicating that the CNS and psychological experience, including stress, produce alterations in the functioning of the immune system. Since much of the psychological change has been defined as stress, a brief discussion about the use of the term "stress" is warranted before proceeding.

The Meaning of Stress

The term "stress" has been used in so many different ways that it immediately presents a semantic nightmare. In this review, our main focus will be on psychological stress rather than physical stresses, such as starvation or exposure to extreme cold, etc. In real life, however, these two different kinds of stress are often interrelated. For example, the physical stress of starvation is accompanied by the psychological stress of hunger and fear of dying. Conversely, the experience of extreme anxiety and/or fear in an animal usually leads to changes in behavior, such as withdrawal or the fight or flight response. In human beings, the range of behavior designed to alleviate anxiety may be far more complicated, including such behaviors as drug-taking, including the use of alcohol and cigarettes, as well as potential changes in dietary and sleep and waking behavior. So, in talking about stress producing somatic change, it is useful to clarify whether stress has produced that change by the CNS causing internal physiological alterations or whether the CNS has created an external, behavioral change which has in turn altered the internal milieu.

Furthermore, the stress itself may not be purely psychological in nature. Obviously, if one used starvation as a psychological stressor, there would be a profound concurrent physical trauma which might compound any psychosomatic effect that such a stress would have. But this question also arises with more subtle stressors. The use of electrical shocks in avoidance conditioning and the use of handling or overcrowding may all produce subtle but important somatic changes. On the other hand, certain stressors which have been used in experimental animals, such as visual, auditory, or olfactory exposure to a predator who cannot physically touch the animals, provide a "purer" psychological stress. Finally, there is often confusion about whether stress is the stimulus or the response. In general, it makes more sense to us to define stress in terms of the stimulus rather than the response which, as others have suggested, might best be called strain. Ultimately, of course, we are more interested in the amount of psychological strain that occurs. The difficulty comes in measuring this, however. For experimental animals, we have no direct way of knowing the animal's inner psychological experience. And in human beings, the same "stressful" stimulus may produce two widely varying responses. Human beings are exquisitely sensitive to the symbolic

meaning of various stimuli which are not physically traumatic, for example, words conveying the death of a child. What is stressful to one person may be a source of pleasure to another. It is beyond the scope of this review to deal with all of the controversy and confusion about the use of the term "stress." However, we will be explicit about the particular definitions of stress used in the individual studies referred to and return to this issue in the section on Methodologic Issues.

Stress and Illness: Clinical Data

The clinical literature and indeed clinical experience has repeatedly emphasized the importance of psychological factors in both the onset and the course of a variety of illnesses known to be influenced at least in part by disturbances in immunity, including cancer (27), infectious disease (28, 29), autoimmune disease (30, 31), and allergy (32). In at least two studies done, one of patients with breast cancer (33) and another of patients with rheumatoid arthritis (34), there have been specific correlations between immunoglobulin levels and emotional states. Both individual case studies and detailed, although retrospective, clinical studies have argued persuasively for the importance of psychological stress in the onset and course of many of these illnesses.

On the epidemiologic side, the measurement of the magnitude of recent life change, developed initially by Holmes and Rahe as a quantifiable measure of stress, has provided further suggestive evidence for the contribution of stress to the development of a variety of illnesses in a variety of different populations (35). In addition, other studies have found an increased incidence of disease in populations experiencing the same major life change, such as bereavement (36) or loss of work (37). These epidemiologic studies would lead us to conceptualize stress as defined by recent life change as a risk factor, increasing the likelihood of disease at a level that is statistically significant but by no means uniformly associated with disease. In this regard, it is important to avoid simplistic notions of stress and psychological experience as the "cause" of disease but rather to view stress as having a complex interaction with the personality and biology of the host and hence with the expression of disease. Further, Cobb and others have shown that if social support is included in the equation, the relationship between stress and disease becomes more sharply defined (38). When social support is high, it tends to protect against the effects of stress; when it is low, it tends to magnify it. With some success other researchers have included different measures designed to evaluate subjects' capacity to cope with stress as a further modifier of this relationship.

Stress and Experimental Illness

Animal experiments have also demonstrated definite but, in many cases, complex effects of stress on disease susceptibility. In this discussion we are again focusing on diseases which are closely linked with failures in immune regulation.

With regard to *infection*, experimental stress, typically created either by physical restraint or avoidance conditioning using electrical shocks, has been associated with increased susceptibility to numerous viral illnesses, including herpes simplex (39), poliomyelitus virus (40), Coxsackie B virus (41), and polyoma virus (42). Other stressful manipulations, such as exposure to high intensity sound (43), overcrowding (44, 45), or exposure to a predator (46),

have also increased susceptibility to certain infections. In the latter study, Hamilton showed that exposure to a predator (cat) dramatically increased the rate of reinfection of mice to tapeworm, and was also correlated with adrenal hypertrophy and splenic atrophy, including an atrophy of splenic corpuscular germinal centers containing high concentrations of lymphocytes.

To add to the complexity, however, it has also been observed in at least two studies that stress may have a protective effect against infection (47, 48). The exact nature of the stress and the timing of its application in relation to a particular organism, as well as the genetics of the host, are all important factors in determining the effect which stress has on susceptibility to infection. Furthermore, the time of exposure to an infectious agent needs to be considered both in terms of the stage of the life cycle and of the diurnal rhythmicity of the host. As pointed out above, a variety of functions of the immune system have a circadian rhythm.

The incidence and rate of growth of experimental animal tumors have been altered by stress. A strain of mice carrying the Bittner oncogenic virus usually develops mammary tumors within 8–18 months after birth. Riley demonstrated that stress, as defined by overcrowding, was associated with a 92% incidence of tumor, whereas only 7% developed tumors in the nonstressful environment (49). Elevated cortisol levels and involution of the thymus gland were also found in the stressed animals. In another study, brief daily handling and mild electric shock, if administered early in life, differentially retarded the rate of tumor development and decreased the survival of rats infected with Walker 256 sarcoma (50). Both the nature of the stress and the exact time of the stress accounted for a significant variability in the response. In yet another study, stimulation by handling during the first 3 weeks of life has been shown to shorten the survival time of mice after transplantation of lymphoid leukemia as compared to unstimulated mice (51).

Adjuvant-induced arthritis in rats has been used as an animal model for rheumatoid arthritis. Amkraut et al. have reported that group housing stress significantly increases the intensity of this disease in male rats and that it also accelerates the time of maximal disease and rate of recovery (52).

Stress and the Immune System

In addition to the more indirect evidence just presented, there is also direct evidence for the effect of CNS change on the immune level.

Cellular Immunity

In both human and animal studies, stress has been associated with alterations in cellular immune mechanisms. In a recent human study, bereavement was found to be associated with depressed lymphocyte function, specifically in T-cell response to mitogens at 5 weeks but not at 2 weeks after a bereavement (53). There was a 10-fold difference in this T-cell function at 5 weeks between the 26 bereaved spouses and the controls. No difference was found in the number of T and B cells, antibody titers, presence of autoantibodies, or in the hormonal studies included. Unfortunately, the report lacks any description of the degree of severity of the grief reactions as well as sufficient detail about the presence of medications or medical illnesses which might have al-

tered their lymphocyte function. Similar depression in T-cell response to mitogens has been noted in astronauts in the sky lab program for the first 3 days in the post-flight period (54). It is unclear, however, whether the apparent impact of splashdown had its effect on the lymphocytes by virtue of psychological stress or by the physical stress of splashdown. Palmblad and his colleagues showed that the stress of a 77-hour sleepless vigil in man, in which exposure to loud noise also occurred, was associated with an increase in interferon production, a function of T cells, as well as a biphasic change in phagocytic activity (55).

Recently attention has shifted to lymphocytotoxicity as an important index of immunocompetence. Two recent papers given at the 1978 Annual Meeting of the American Psychosomatic Society cited data in human beings linking stress and immunosuppression as measured by lymphocyte cytotoxicity. In one study, Greene and his colleagues from Rochester, N.Y., demonstrated a statistically significant correlation between increased stress as defined by life change units combined with a high vigor score on the profile of mood states (POMS) and a decrease in lymphocyte cytotoxicity (56). They hypothesized that the high vigor score reflected denial used as an unsuccessful coping mechanism in the face of increased stress. In a similar study reported at the same meeting, also involving college students, Locke and colleagues found a statistically significant correlation between high stress combined with poor coping and a decline in natural killer activity (57). In Locke's study, no significant correlations between stress and various parameters of humoral immunity were found. Natural killer activity provides a particularly interesting index of immunocompetence for several reasons. First, although its precise function is unknown, it is thought to provide a general host defense in combating host cells undergoing malignant transformation and also against viruses (58). Secondly, what is measured is a natural property of the cell rather than an artificially induced measure, such as response to mitogens. For these reasons, it appears to have particularly important implications for resistance to disease. Its disadvantage is that it is not as yet as well standardized as mitogen stimulation techniques. Although all of these studies reporting suppressed cellular immunity in human subjects under stress are intriguing, none has been replicated at this point, although no attempts have yet been reported, either.

Giving further credibility to these human studies, there have been several animal studies in which stress has also been associated with diminished lymphocyte response to mitogens (59, 60), lymphocyte cytotoxicity (59), and lymphocyte response to antigenic stimulation (61). In related animals studies, suppression of cellular immunity secondary to stress has been reflected in diminished skin homograft rejection in mice (62), diminished graft-versus-host response (63), and diminished delayed hypersensitivity reaction (64).

Whereas most studies have thus concurred in the immunosuppressive effects of stress on cellular immunity, a few have found conflicting results, in which stress appears to have augmented cellular immune function (59, 65, 66). For example, one study reported that stress increased delayed hypersensitivity. Although the discrepancy may be explained in part on the basis of differences in the experimental animals and the type of stress used, the duration of stress and the length of the

time interval between the stress and the immunological measurements are of central importance. For example, Monjan and Collector subjected mice to the stress of loud noise on a chronic basis and found a biphasic response (59). For the first 2 weeks or so of stress, they found a 50% decrease in response to mitogens and lymphocyte cytotoxicity. After 3 weeks, however, there was a striking increase in these same functions. These investigators attribute the initial decrease to the increased steroid levels occurring over the same period. They attribute the longer-term increase to one or more circulating factors, such as somatotropic hormone. Similarly, Folch and Waksman demonstrated that either a noise stress, a water deprivation stress, or an injection of hydrocortisone may all result in loss of rats' suppressor T-cells adhesiveness to glass wool (a measure of suppressor T-cell activity) *in the short run*, i.e., around 5 days. However, at 2–3 weeks, there is a return to normal levels, followed by a marked increase in suppressor cell activity. Like Monjan and Collector, they attribute the short-term effect to elevated steroids, but wonder whether the subsequent increase is due to altered levels of thymus hormone(s) or a redistribution of lymphocytes (66).

Humoral Immunity

A variety of experimental stresses, especially overcrowding, have also been shown to reduce antibody responses to flagellin, a potent bacterial antigen, both on primary and secondary immunization (67–69). If the stress is applied prior to or immediately subsequent to immunization, it is immunosuppressive, and only if small doses of antigen are used. However, if stress is applied several days after inoculation, it is ineffective (70).

Early Experience and Immunity

The effect of stress in early life experience has also been associated with altered immunological responses later in life. Adult rats which had been handled in infancy have been shown to have higher antibody titers in response to both primary and secondary immunization with flagellin than a control group (71). In contrast, handling 1 week prior to immunization has been found to depress antibody responses to immunization. Once again that reenforces the concept that the timing of the stress is crucial. Early infections and nutritional stresses can also modify the developing immune system and lead to permanent alterations in both the immunological responses and host substances as summarized in a recent article by Dutz and colleagues (72). Residual immunologic alterations persisting long after proper nutrition was resumed were described in phagocytosis, complement levels, cyclic AMP, accelerated thymic atrophy, and an accelerated decline in cell-mediated immunity.

CONDITIONING AND THE IMMUNE SYSTEM

Another link connecting the psyche and immune system has been the demonstration of behaviorally conditioned immunosuppression. In 1975, Ader and Cohen described the phenomenon of behaviorally conditioned immunosuppression in rats using a taste aversion paradigm (73). Saccharin (the conditioned stimulus) was paired with cyclophosphamide (the unconditioned stimulus), a substance producing gastrointestinal distress as well as immunosuppression. In a carefully controlled study, subsequent

exposure to saccharin was found to exert an immunosuppressive effect as measured in lower antibody titers raised to immunization with sheep red blood cell antigen. We have been able to replicate the phenomenon of behaviorally conditioned immunosuppression (74). The reason for this effect remains a mystery. However, it does not seem to be due to a nonspecific stress. When lithium chloride is substituted for cyclophosphamide, no immunosuppressive effect is seen. Furthermore, in the same paradigm, adrenocorticoid levels are equally raised by exposure to saccharin regardless of whether lithium chloride or cyclophosphamide is used as the unconditioned stimulus (75).

HYPNOSIS AND THE IMMUNE SYSTEM

Hypnosis has been found to alter the clinical manifestations of delayed hypersensitivity. Black and his associates were able to inhibit the Mantoux reaction (tuberculin skin test) by direct suggestion under hypnosis in subjects known to be positive reactors (76). Although the typical swelling and erythema were absent, skin biopsies did reveal the expected degree of cellular infiltration. In other studies, direct suggestion under hypnosis has been shown to inhibit immediate hypersensitivity reactions in allergic dermatitis (77), allergic responses to food (77), and in urticarial eruptions (78). There have as yet been no adequate attempts to replicate these interesting studies.

BRAIN STIMULATION AND THE IMMUNE SYSTEM

By directly stimulating the brain, different investigators have produced alterations in the immune response. Lesions in the dorsal hypothalamus of rabbits have been shown to suppress both humoral and cellular immunity (79). The same Russian authors have described the effect of mesencephalic stimulation in enhancing antibody responses (80). Fessel and Forsyth demonstrated a doubling of gamma globulin levels by electrical stimulation of the lateral hypothalamus in rats (81). Bilateral hypothalamic lesions in guinea pigs have been observed to protect against lethal anaphylaxis (82, 83). In further studies, it was found that anterior but not posterior lesions protect against anaphylaxis (84). In addition to demonstrating the protective effect of anterior hypothalamic lesions against anaphylaxis, Macris and his colleagues found that they lowered antibody titers and decreased cutaneous delayed hypersensitivity by this technique (85). Stein's review in *Science* (3) contains a more detailed discussion of the effect of hypothalamic lesions on immunological reactions and evidence for the role of hormonal mediation of these effects.

THE QUESTION OF MECHANISMS

There seems little doubt that different psychological states and CNS stimulation can influence the immune system. The questions now are really what the mechanisms are, and how clinically significant they might be.

The predominant hypothesis has been that CNS change leads to immunologic change through the mechanism of *hypothalamic-pituitary hormonal* stimulation. There is considerable evidence, direct and indirect. Already mentioned are the variety of hormones which directly af-

fect immunity. Adding those interactions with our growing knowledge of psychoendocrinology (86) provides strong indirect evidence for the importance of this mechanism. Not surprisingly, adrenocorticoids have been focused on the most. In at least two studies involving stress and immunity, simultaneous elevations in corticosterone have been measured which correlate with the immunological depression (49, 60). Thyroid hormone has also been implicated.

Another mechanism may involve the *autonomic nervous system*. The use of hypnosis to inhibit the Mantoux response affected the vascular component of the reaction. Clearly the autonomic nervous system is exquisitely sensitive to emotional states and may at least affect many of the secondary aspects of the immune response. Adrenergic nerve endings can be found in the spleen and in the thymus and may have a more direct relationship on immunologic reactivity. In fact, a recent study by several Japanese investigators reports a suppression in a primary immune response (in both antibody titer and number of plaque-forming cells) after chemical sympathectomy in mice by the use of 6-hydroxydopamine (87). There is also the possibility, since lymphocytes have β-adrenergic receptors, that sympathetic release of adrenalin can modify cellular immunity. A recent report provides evidence that chronic β-adrenergic stimulation over a period of several days decreases the number of β-adrenergic receptor sites on polymorphonuclear leukocytes (88).

Finally there is the possibility of a *separate mechanism of action*. The phenomenon of behaviorally conditioned immunosuppression provides some support for this. The fact that the taste aversion conditioned stimulus, saccharin, has an immunosuppressive effect cannot be fully explained by changes in corticosteroids. Further, the data from Besedovsky's study, showing an increased rate of neuronal firing in the hypothalamus immediately after antigen antibody interaction and prior to any change in thyroid or corticosteroid hormone, are also suggestive of a direct link between an immune reaction and the CNS (25). In the latter case, it appears to be an afferent link beginning with the immune reaction somehow sending a message to the hypothalamus. The investigation into possible mechanisms is clearly only in its infancy. Hopefully, our colleagues in immunology will share our enthusiasm in the pursuit of these questions.

METHODOLOGIC ISSUES

In reviewing the data already available and in considering future approaches to research in this field, several points about methodology need emphasis.

First, since the term "stress" in all likelihood will continue to be used to describe diverse phenomena, overgeneralization is to be avoided. Instead, careful attention should be given to what it actually refers to in any given situation and how it is quantified. In attempting to delineate mechanisms of action we need to be aware that what is defined as stress, even psychological stress, may often include direct physical stimulation that is inherently noxious. Further psychological stress may change the behavior of an organism such that other physical stimuli come into play which may produce internal physiological change through separate mechanisms. For example, it would be hard to find a person in an extreme state of stress whose pattern of daily liv-

ing is not in some way altered in response to the stress.

That raises the question as to whether a variety of behaviors can influence the functioning of the immune system. There are no data at present about the effect of changes in sleep, diet (short of gross malnutrition), or exercise on immunity. However, there is suggestive evidence that smoking (89) and alcohol consumption (90) can impair some functions of immunity. Beyond that, many experiences like pregnancy and anesthesia (91), for example, and a wide range of drugs including chlorpromazine (92), diphenylhydantoin (93), and some antibiotics (94) may temporarily depress cellular immunity. The list of substances and circumstances which can produce immunosuppression is impressive as even a rapid perusal of the *Index Medicus* can attest. From a methodological point of view, the influence of these other factors, aside from psychological stress, needs to be controlled and in some cases investigated in their own right.

The issue of time and timing is important. At what time does the psychological stress occur? How long does it last? In terms of the life cycle of the host, is it during early developmental periods, in mid-life, or in old age? At what point during a diurnal cycle, during which there are known to be wide variations in certain properties of the immune response? The more information that develops about the normal regulation of the immunological activity, the more sophisticated our hypotheses linking psychological change and immunological change need to be. Illness may occur as a result of a disruption of a normal rhythmic balance rather than an absolute lowering of the various measurements of immune components. There may be biphasic changes depending on the time at which immunologic levels are taken. The discoveries described above require that the hour or perhaps the day in which immunological measurements are made need to be kept as constant as possible, and perhaps single measurements are woefully inadequate.

Finally, we have to deal with the *immune system as the complex network* that it is, in which psychological stress might be either immunosuppressive or enhancing of some aspects of the immune response, depending on the time of measurement and depending on the functions measured. We know that there are subsets of T lymphocytes, both helper T cells and suppressor T cells, and new subsets being identified all the time. Psychological change may produce different effects on these subsets, as hydrocortisone is known to do. Suppression of suppressor cells may enhance certain functions of immunity. Furthermore, higher levels do not necessarily mean a stronger, healthier response. The immune system itself is carefully regulated. Processes are initiated and turned off by feedback mechanisms. Most important is the concept of the homeostasis of the system and the healthy regulation of immunity which gives us a better parameter for susceptibility to disease than the magnitude of a single isolated immune function.

SUMMARY

We have reviewed various sources of evidence which indicate that the immune system, and hence susceptibility to a wide variety of diseases, is subjected to the influence of stress and other psychological states. We have emphasized as well that the immune system is influenced also by genetics, aging, and a variety of environ-

mental experiences. The impact of psychological stress must be evaluated within this broader context and there is a need to know a great deal more about the dynamics and base line of the immune system and its components.

Considerable evidence indicating the close interrelationship between the endocrine and immune system has been presented. Both play key roles in maintaining an organism's integrated adaptation to the environment. It is likely that stress exerts most, but perhaps not all, of its influence on the immune system through the mechanism of endocrinologic change. The autonomic nervous system and possibly other brain-immune system connections may mediate these effects.

The importance of periodicity as one of the most fundamental and ubiquitous properties of all dynamic living systems has also been emphasized. An individual's response to environmental stimuli will vary in a predictable manner according to the amplitude, phase, or even the frequency of various biological rhythms. Stress may disturb the coordinated coupling of such rhythms more than any single dimension.

In future investigations of the effect of stress on immunity, measurements of immunologic function will need to capture the dimensions of time and rhythm more carefully, as well as to control for the many other factors which may cause perturbations in the immune system.

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