American Handbook of Psychiatry

DISORDERS OF IMMUNE MECHANISMS

Raul C. Schiavi
Marvin Stein

Disorders of Immune Mechanisms

Raul C. Schiavi and Marvin Stein

e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 4* edited by Silvano Arieti, Morton F. Reiser

Table of Contents

Disorders of Immune Mechanisms

In recent years immunology has progressed from description of the immune reaction to cellular and molecular analysis of the underlying mechanisms. The fields of microbiology, biochemistry, and biophysics as well as other biological disciplines have developed and applied specialized quantitative techniques which have led to the understanding of immune processes at the organ, tissue, cellular, and subcellular levels. Immune phenomena were initially considered in relation to infectious diseases, and as having a protective and adaptive function. As more knowledge was gathered, it appeared that immune mechanisms may also be involved in the development of various pathological states. Allergic disorders were among the first to be considered as pathological manifestations of immune processes. Since 1950, with the explosive expansion of information and techniques in the field of immunology, considerable data has been acquired, indicating that immune processes are involved in a wide range of pathological and clinical disorders, including autoimmune diseases, neoplasia, and organ transplants. Although clinicians now have an increased understanding of the immunological basis of a variety of illnesses, little attention has been paid to the psychophysiological aspects of immune processes. The immune system, similar to the nervous and endocrine systems, plays an important role in biological adaptation, contributing to the maintenance of homeostasis and to the establishment of body integrity. The similarity between the function of

the immune and central nervous systems maintaining the integrity of the organism in relation to the external environment has recently been pointed out by Salk.

The observation that emotions modify host resistance to infection and that they may influence the development and course of some hypersensitive reactions and autoimmune and neoplastic diseases have led some investigators to propose that immune processes play a significant role in the mediation of psychological influences in some physical illnesses. This chapter will review clinical and experimental findings concerned with the influence of psychosocial processes on immunological reactions. There is an extensive literature in the area of serum proteins and immunological responsivity in psychiatric disorders which has been recently reviewed; these data will not be presented here.

Immune Response

Before considering specific immune disorders, it is important to have an understanding of the concepts of immune response. The immune response may be thought of as a complex specialized reaction developed against foreign proteins or polysaccharide substances known as antigens. The response is specific for each antigen and usually becomes more intense and highly specific with each repeated exposure to the specific antigen.

Immune responses consist of an afferent phase, a central phase, and an effector phase. The borders between these various phases are not clearly delineated. During the afferent phase antigen is processed and identified as foreign; during the central phase various processes occur primarily in the lymphoid tissues which amplify the recognition signal; and in the effector phase appropriate cells are mobilized to react against the antigen. The response may be recognized at the effector level either as specific humoral antibodies elaborated by lymphoid cells, or by an action of specific cells (e.g., lymphocytes or macrophages) on the relevant antigen. Circulating antibodies are usually produced in response to a soluble antigen, whereas cell-mediated immunity develops in response to an antigen fixed in the tissue. The humoral antibody response and the cell-mediated response will be briefly reviewed.

Humoral Antibody Response

Soluble antigen passes to the medulla of lymph nodes or the red pulp of the spleen where it is taken up by macrophages. These cells then appear to send a message to plasma cell precursors, which lie in close proximity to the macrophages at the cortico-medullary junction of lymph nodes and in the red pulp of the spleen. The plasma-cell precursor, probably lymphocytes, proliferate into antibody-producing cells (plasma cells). Plasma cells contain all of the systems required for the synthesis and secretion of proteins. This class of proteins produced by plasma cells is known as antibodies since they

react directly with antigens. They are primarily 7 globulins and, because of their immunological function, are referred to as immunoglobulins. There are at least five classes and several subclasses of immunoglobulins in man. The three major classes are designated IgM, IgG, and IgA.

The IgM antibodies are extremely efficient in binding to particulate antigens such as bacteria and erythocytes, but not as efficient in binding to particulate antigens, such as toxins. The IgG system can bind to soluble antigens, and antibodies are produced for long periods of time. The cells of the IgA, and perhaps of the IgE system, produce molecules capable of binding to skin and mucous membranes. Reagins which have been classified as IgE antibodies are associated with anaphylactic phenomena such as hay fever and asthma. After the interaction of antigen and IgA or IgE antibodies, histamine and other pharmacological agents are locally released.

Cell-Mediated Immune Response

If antigen is fixed in tissues, such as a tissue homograft, or in a modified part of the body's own tissues, such as skin treated with a simple chemical sensitizing agent, the response is of a different type than that of the humoral antibody response. It appears that small lymphocytes passing through the tissues are sensitized peripherally and then pass down to a local lymph node where they enter the free area of the cortex follicles. The small lymphocytes

proliferate at this point and become differentiated into large cells with easily identifiable characteristics. After a few days some of the lymphocytes become immunologically active leaving the local lymphoid tissue to go to other lymph nodes where other immunologically active lymphocytes are propagated. At this point, the immunologically active cells can be found in the peripheral blood and pass to the graft where they can initiate the process of graft rejection or react with an antigen deposit in peripheral tissue to produce an inflammatory response such as that which occurs in chemical contact sensitivity or the tuberculin reaction. Immunological responses carried out by sensitized cells in the absence of circulating antibody include delayed sensitivity, transplantation immune reactions, and various autoimmune phenomena. The cellular systems capable of carrying out these processes may form part of a surveillance system the function of which may be to eliminate cells arising as a result of mutation, e.g., neoplastic cells.

Infectious Diseases

The concept of multiple causation of disease is well illustrated by the observation that colonization of an organism by bacteria does not necessarily result in illness. Clinically, it has been noted for many years that infectious diseases are the result of host-microorganism interaction. In order to understand the disease process, it is necessary to investigate the aspects which determine the capability of the microorganism to initiate infection and

those which influence the host response to the infection. A great deal of attention has been devoted clinically and in the laboratory to the identification of microorganisms involved in infectious diseases and there has been growing interest in the factors which modify host resistance. Among these, psychosocial influences have been shown to play a role in infectious diseases. For example, several studies have shown that psychological variables influence the rate of recovery from infectious mononucleosis and influenza, and the development of lesions due to herpes simplex virus. Psychological factors have also been demonstrated to modify the onset and course of pulmonary tuberculosis and experimentally it has been shown that the tuberculin reaction can be inhibited by means of hypnosis.

There are, however, few data regarding the physiological mechanisms involved in the mediation of psychological factors on host resistance in man. The study of Meyer and Haggerty represents one of the few attempts to consider immune variables in relation to psychological influences on infectious diseases. They studied prospectively members of sixteen families for a one-year period with systematic throat cultures for β hemolytic streptococci, periodic measurement of anti-streptolysin-O-antibody titers, and clinical evaluation of illness. It was found that acute or chronic family stresses not only were important factors determining whether the individual became a host for the streptococcus, or became ill following colonization, but also that psychological stress influenced the proportion of persons in whom

there was a rise of antistreptolysin O following infection.

In addition to clinical observations, there is a growing body of experimental data supporting the hypothesis that psychosocial factors play a role in infectious diseases. Rasmussen and collaborators, in an extensive series of studies, have primarily employed avoidance-learning procedures as the experimental model for investigating the effects of psychological stress. This procedure requires mice to jump a barrier once every five minutes at the presentation of a signal to avoid an electric shock delivered to their paws, a response the animals quickly learn to perform. Daily exposure for six-hour periods to these conditions resulted in an increased susceptibility to herpes simplex virus, poliomyelitis virus, coxsackie B, and polyoma virus infection. Physical restraint also was found to increase the susceptibility of mice to herpes simplex virus," while high-intensity sound stress resulted in a transient diphasic susceptibility pattern in mice inoculated intranasally with vesicular stomatitis virus. In monkeys acute avoidance stress was found to decrease their susceptibility to poliomyelitis. Social factors such as the effect of differential housing have been studied, and it has been shown that mice housed alone were significantly more susceptible to encephalomyocarditis virus and less susceptible to Plasmodium berghei than animals housed in groups.

In summary, both clinical and experimental observations demonstrate

that psychosocial factors influence infectious diseases. The experimental procedures which have demonstrated psychosocial influences on host response to infection have also been shown to modify a variety of immune processes. These studies will be reviewed in a later section.

Allergic Disorders

Hypersensitivity refers to a state of enhanced reactivity to a foreign substance acquired by previous exposure to the same or a related substance. Allergy is frequently used synonymously with hypersensitivity and has come to be considered a clinical state in which individuals react in an intense and frequently injurious manner to a substance that usually has no effect on most people. A wide range of antigens are capable of inducing the hypersensitive response and the term allergen is used generically. Hypersensitive reactions are of two major types. Immediate hypersensitivity in which the response takes place within seconds or moments after exposure to the allergen and is always associated with humoral antibodies. This type of reaction occurs in anaphylaxis and in various allergic clinical states such as asthma, hay fever, eczema, and urticaria.

The other type of hypersensitive reaction occurs two to three days after exposure to the antigen and is referred to as delayed hypersensitivity. In this reaction there are no humoral antibodies, and it is a cell-mediated immune

response. As mentioned earlier, the tuberculin reaction typifies delayed hypersensitivity. Clinically, contact allergy occurring in response to poison ivy, poison oak, or contact with certain drugs is a manifestation of a delayed hypersensitive reaction.

Considerable clinical evidence suggests that psychological factors are related to the precipitation of many allergic disorders including bronchial asthma. The literature on the role of psychological influences on bronchial asthma is reviewed in Chapter 28 of this volume and the present discussion will focus only on the relationship of emotional factors to allergic processes in general.

It has been repeatedly demonstrated that periods of life change and stress antedate the onset of many allergic episodes and that a variety of emotional states may trigger the onset of symptoms. Sensitivity to allergens has not been demonstrated to be quantitatively stable with time and in a number of instances it has been demonstrated to increase in association with emotional distress. More than twenty years ago, Holmes et al. demonstrated that naturally occurring and experimentally induced emotional distress enhanced the intensity of allergic rhinitis and the magnitude of the response of the nasal mucosa of patients with hay fever exposed to a standard amount of pollen. The evidence suggested that parasympathetic activity mediated the psychological influences in the nasal mucous membranes. Since that time, a

body of information has been gathered from the fields of pharmacology, immunology, and pulmonary physiology, substantiating the influence of the autonomic nervous system on vascular, mucosal, and muscular changes occurring in target organs during the hypersensitive reaction. Mediating mechanisms involved in the precipitation of at least some allergic and asthmatic episodes probably include the autonomic and endocrine systems interacting with allergic inflammatory processes. It has been postulated that increased parasympathetic activity leading to broncho-constriction and to an increase in bronchial mucous secretion mediates behavioral influences in the precipitation of asthmatic attacks.

Several investigators studied the relationship between psychological factors and biological susceptibility as two sets of independent variables predisposing to allergic illnesses. The results have shown that both emotions and immune mechanisms contribute to the development of susceptibility to allergy although the mode of interaction is still unclear. The findings have also suggested that failure to take into account the immunological heterogeneity of allergic patients may have been one important source of inconsistency in earlier psychosomatic investigations.

Implicit in a number of psychological studies of hypersensitive patients is the possibility that emotional factors not only interact with an already established allergic substrate, but that they may also directly influence the

development of an allergic diathesis. There is, at present, no solid clinical evidence; limited experimental data will be reviewed later.

Autoimmune Diseases

It is well known that antibodies are not usually developed against an individual's own tissues. Burnet and Fenner emphasized this phenomenon when they discussed the concept of self-recognition, i.e., the ability of the mechanisms responsible for antibody production to distinguish "self" from "not self." In view of the previous discussion of the immune response, the formation of antibodies which would react with the body's own tissues would be extremely destructive. Usually a substance is only antigenic when foreign to a specific organism. In rare instances cells are antigenic in the organism from which they arise. The antibodies which develop are known as autoantibodies and the immunizing process is referred to as autoimmunization. Autoimmune disease is defined as an illness in which autoantibodies or a sensitized lymphocyte reacts with host tissue. It is important to note that there is no conclusive evidence indicating that the autoantibody or lymphocyte is the causative agent. Autoantibodies could be causative, a result of autoimmune disease, or only a concomitant part of the illness.

It has been suggested that autoimmunity is a result of immunologic

hyperactivity in response to the release of a sequestered antigen or due to proliferation of “forbidden clones” of antibody-producing cells. Both of these theories have been thoroughly discussed. Another hypothesis is that autoimmune disease is a result of a state of immunological deficiency, and several theories have been proposed to explain the pathogenic mechanism of the deficient state. Among these is the suggestion that a latent virus, mycoplasma, or bacterium may become pathogenic and alter the immunological mechanism resulting in the production of autoantibodies. The autoantibody may be an attempt of the organism to protect itself and may not represent the primary pathogen.

A number of clinical entities in man are now considered to be autoimmune diseases and include systemic lupus erythematosus, rheumatoid arthritis, chronic glomerulonephritis, thyroiditis, and hemolytic anemia. In addition, autoimmunity has been implicated in the pathogenesis of scleroderma, myasthenia gravis, and ulcerative colitis. There is evidence strongly suggesting that the tissue in rheumatoid arthritis is involved in a chronic immune response. The profuse lymphocytic infiltration of synovial tissue in rheumatoid arthritis and the immune complexes found in the synovial fluid support this hypothesis. The specific aspects of the altered cellular antigen have not as yet been demonstrated, but a chronic viral infection is one of the major possibilities. It is likely that one of the many viruses capable of slow atypical infection may modify the antigenicity of the

synovial cells and result in an immune reaction. It has been speculated that a similar immune process is involved in other collagen vascular diseases such as scleroderma, dermatomyositis, and systemic lupus erythematosus.

Solomon has reviewed the extensive literature concerned with the psychophysiological aspects of autoimmune diseases. Among autoimmune diseases, rheumatoid arthritis has been the disorder most frequently considered in psychosomatic investigations. Several investigators have studied the influences of psychosocial factors in relation to rheumatoid arthritis and have assessed personality traits in arthritic patients. Although no consistent personality pattern in rheumatoid patients emerges from these studies, the findings convincingly document the importance of emotional factors in the course of the disease. Patients have been described as predominantly perfectionistic, self-conscious, introverted, and inhibited in relation to various comparison groups. Moos and Solomon in a controlled study found that patients with rheumatoid arthritis were significantly more masochistic and self-sacrificing and showed difficulties in recognizing and expressing hostility. They also studied the relation between psychological factors and rapidity of progression of the disease, and functional incapacity and response to medical treatment. Patients with poor prognosis and less satisfactory response were significantly more anxious and depressed, and demonstrated more social alienation and less adequate coping and adaptive mechanisms.

Several authors have drawn attention to similarities in the role of psychological factors in patients with rheumatoid arthritis and patients with other autoimmune disorders. Stressful life events, such as the loss or threatened loss of a significant relationship, were reported to precede not only the onset of rheumatoid arthritis, but also of systemic lupus erythematosus. Furthermore, similarities were found in the personality characteristics of patients with these two disorders. Patients with ulcerative colitis, a disease in which anticolon antibodies have been demonstrated, have also been described as showing certain obsessive-compulsive traits which resemble to some degree the personality factors described in arthritic patients. The meaning of personality factors in the various autoimmune disorders is, however, not certain and requires further study.

Solomon has advanced the theory that the central-nervous-system control of immune mechanisms plays an important role in the mediation of the effect of psychological factors in autoimmune disease. This theory rests on evidence that autoimmune diseases are the result of a state of immunological incompetence, and it has been proposed that the immune deficient state may be the consequence of the activation of the adrenocortical system due to emotional influences. A deficient immunological state may prevent elimination of self-reacting immunologic competent cells, or it may permit the formation of soluble antigen-antibody complexes resulting in the production of tissue injury and inflammation.

Organ Transplants

In the 1960s, considerable progress has been made in the area of organ transplantation and there are a number of excellent reviews which consider the immunological aspects. The greatest success has been with the kidney, while transplantation of other organs e.g., liver, heart, or lungs, has been far less successful. A great deal of attention has been paid to the mechanisms responsible for failures in the acceptance of grafted organs. Peter B. Medawar and his co-workers were the first to demonstrate that the homograft reaction is mediated by immune mechanisms. It has been demonstrated that skin homografts are rejected by the cell-mediated immune response as described earlier. The rejection of other grafts such as the kidney involves both humoral and cellular immune mechanisms. Hume has described the mechanism of primary acute rejection of the kidney. Antigens migrate from the donor kidney to local lymph nodes where they encounter immunocompetent plasma cells. In the lymph node humoral antibodies and sensitized lymphocytes are produced and migrate back to the donor kidney. The sensitized lymphocytes and humoral antibodies react to the kidney cells resulting in the characteristic pathological features of the rejection crisis. Progress has been made in the use of immunosuppressive agents which inhibit the immune mechanisms involved in organ rejection while leaving all other immune responses intact.

Attention has also been drawn to the role of psychosocial factors in relation to organ transplantation. It has been shown experimentally that in mice subjected to chronic avoidance learning, there is a prolongation of skin homograft survival time. This effect is probably mediated by a modification of immune mechanisms as a result of the psychological stress produced by the avoidance learning.

Clinically, some investigators have reported that stressful life events, intense anxiety and depression precede some rejection crisis following renal homo-transplantation. Patients who died following kidney transplantation were observed to experience feelings of abandonment, emotional tensions, and grief to a degree not evidenced among patients who survived. Various pathophysiological processes may be directly responsible for the patient's death, including disturbances in electrolyte balance, hemorrhage, cardiovascular complications, and infection. The possibility that immune processes may participate in some rejection crises associated with psychological trauma deserves consideration. At present, however, there are no data reported in this regard.

Cancer

The natural history of neoplastic diseases is in many ways similar to the interaction between host and microorganisms in infectious diseases. The

genetic characteristics of both participants, as well as a variety of internal and external factors, determine the outcome of the relation between the host and living pathogenic cells. There is a growing body of knowledge that immune mechanisms may be involved in both the development and outcome of neoplasia. It has been shown that many experimental cancers in animals contain new antigens. In addition, it has also been demonstrated that the majority of carcinogenic agents decrease the overall immunological capacity before the onset of cancer. There are many reports suggesting immunological deficiency in man as a prerequisite for progressive neoplasia. It is of interest that the relation of immunological mechanisms to cancer has been further supported by some observations on immunosuppressive techniques utilized in organ transplants. It has been found that there is a marked increase in the incidence of tumors in approximately 6-8 percent of transplant patients maintained on immunosuppressive drugs. Furthermore, it appears that in some instances when the immunosuppressive treatment is stopped, the tumors that developed while on immunosuppression rapidly regress.

As pointed out above, a variety of internal and external host factors appear to play a role in the development, course, and outcome of neoplastic disorders. Among these factors psychosocial influences have been shown, both experimentally and clinically, to be determinants in neoplasia.

Experimentally, considerable evidence demonstrates that early

experiential factors not only have a profound influence on behavior and on the endocrine and immunological responsiveness of small mammals, but that they also influence the development and course of experimentally induced cancer. Furthermore, the findings show that the outcome of the relation between the host and the neoplastic process depends upon the species and the nature of the experimental intervention. Brief daily handling and mild electric shock administered early in life, for instance, modify the rate of tumor development and the survival of rats injected with Walker-256 sarcoma. Infantile stimulation also shortens the survival time of mice after transplantation of lymphoid leukemia, but does not modify the mortality rate of murine leukemia virus. Similarly, differential housing and sex-segregated groupings modify the incidence of mammary carcinomas in mice, decrease the survival time to injections of subcellular leukemia material, but do not influence the development of Walker sarcoma tumors.

Clinically, a number of investigators have reported a relationship between certain premorbid factors and personality types, and the development of cancer. Kissen and collaborators, for example, have conducted an extensive series of studies on the role of personality factors in lung cancer. They have repeatedly observed that lung cancer patients have less ability for emotional discharge than noncancer patients, as assessed clinically and measured by the Maudsley Personality Inventory. In addition, they have found significant differences between the same lung-cancer

patients and controls in the reported incidence of certain environmental factors such as adverse episodes in childhood and adulthood. Bahnson and Bahnson also have claimed that certain features such as depression, denial, and repression exist to a pathological extent as premorbid characteristics in patients with cancer.

By and large, the studies concerned with premorbid factors in cancer are retrospective in nature and, therefore, are limited by the inability to control for distortions due to the effect of immediate precipitating factors and the psychological impact of the disease. Some investigators have focused on the role of emotional factors during the immediate premorbid phase. Their findings have demonstrated that depression, hopelessness, inability to express hostile feelings, and object loss may play an important role in influencing the onset of the neoplasia or the course and outcome of the disease. An illustrative example is given by an interesting predictive study conducted by Schmale and Iker on fifty-one females with cervical cellular cytology, indicating suspicion of cervical cancer identified during routine screening procedures. The investigators were able to make a significantly high number of correct predictions regarding the diagnostic outcome of cone biopsy of the cervix, based on the clinical assessment of feelings of hopelessness during the previous six months. Assuming that a causal relationship exists between emotional factors and the onset and development of neoplasia, a question that has attracted considerable interest is concerned

with the nature of the physiological processes involved. The growing information on the immunological aspects of cancer raises the possibility that immunological mechanisms play an important role in the mediation of emotional influences on susceptibility to neoplastic disease. The extensive literature on the psychophysiological aspects of cancer has been thoroughly reviewed.

Psychosocial Factors and Immune Processes

It is of considerable interest that some of the psychosocial situations, which have been demonstrated to modify the susceptibility to infection and the development of neoplasia, have also been found to have a profound influence on immune processes. Avoidance learning, for example, decreases the susceptibility of mice to passive anaphylaxis. Overcrowding, but not the stress of electric shock, initiated prior to immunization of rats with flagellin, a bacterial antigen, reduced both the primary and secondary antibody response. Vessey found that grouped mice have significantly lower titers of circulating antibodies than isolated mice and, by identifying social rank, he demonstrated that dominant mice had higher titers than the other mice in their groups. In primates, exposure to a complex pattern of visual, auditory, and somasthetic stimulation was observed to increase plasma cortisol levels markedly and to decrease the circulating antibody response to immunization with bovine serum albumin. A number of reports in the Russian literature

have considered the effect of psychological mechanisms on antibody titers. Petrovskii, for example, studied changes in agglutinin titers associated with behavioral disturbances induced in immunized dogs and baboons by stressful stimuli or by conflict-conditioning techniques. He observed a parallelism between the intensity and duration of the behavioral disturbances and the fall in circulating antibody titers. It is to be noted that under certain conditions psychological stimulation can enhance the immune response. Brief handling of rats, for instance, during the preweaning period was found to increase both the primary and secondary antibody response to flagellin immunization.

The physiological mechanisms which mediate the psychosocial influences on host resistance are complex and in need of further clarification. It seems reasonable to speculate that the demonstrated effect of psychosocial stress on the modified susceptibility to some viral infections and neoplastic processes may be due to the suppression of immediate and delayed hypersensitive mechanisms.

There is evidence that the hormonal and reticuloendothelial systems are involved in the mediation of psychological influences. Avoidance learning or confinement is accompanied by adrenal hypertrophy, lymphocytopenia and a slowly developing involution of the thymus and spleen occurring in temporal relation with the increase in susceptibility to viral infection. The pituitary-adrenocortical system which is known to be altered by psychosocial

stimulation, has been the focus of considerable attention because of evidence primarily derived from pharmacological studies that adrenal steroids may modify susceptibility to infectious disease, alter immune reactions, or depress inflammatory responses. In addition, both psychological stress and adrenocortical steroids have been reported by some investigators, although not by others, to suppress interferon production, a nonspecific protein directly involved in host resistance to viral infection.

Whether changes in endogenous adrenal hormones, occurring in response to environmental stimulation, are responsible for some of the effects of host resistance and immune processes requires further analysis in the context of the different experimental models investigated. Based on studies conducted with stressed, adrenalectomized animals, it appears that adrenal steroids are responsible for the increased resistance to passive anaphylaxis, while the retarded rate of disappearance of vesicular stomatitis virus from the site of inoculation and the increased susceptibility to this viral agent seems independent of adrenal activity. These findings clearly demonstrate the complexity of the field.

Little information is available on the role played by other hormonal systems and physiological processes in the mediation of psychological and environmental stimulation. Probably only after careful elucidation of the physiological correlates of psychosocial intervention and their interaction

with the pathophysiological processes underlying a given pathogenic stimulus, will it be possible to predict the response of an organism to specific experimental conditions.

The Central Nervous System and Immune Processes

Recently the neurophysiological mechanisms that might mediate the psychosocial influences on immunological reactions have been experimentally studied. At the turn of the century the central nervous system (CNS) was considered to be involved in the development of immune phenomena. The brain was thought to be the target organ initiating the anaphylactic reaction. A series of studies conducted between 1910 and 1920 demonstrated, however, that the characteristic signs of anaphylaxis could occur in decerebrated guinea pigs and dogs. With the development of immunological and biochemical techniques, an impressive amount of knowledge on the cellular and chemical aspects of immune processes was acquired, and the participation of the CNS was largely overlooked. The consideration of the integrative capacity of the CNS on a variety of physiological processes has stimulated a renewed interest in the role of the CNS in immune processes.

Studies of the effect of sectioning the spinal cord on immunogenesis have shown changes such as decreased antibody formation following

sensitization and lowered histamine sensitivity. These findings may be the secondary result, however, of peripheral disturbances in temperature control and blood circulation.

The effect of midbrain lesions on the course of anaphylaxis in the guinea pig has been investigated by Freedman and Fenichel. Bilateral electrolytic lesions at the level of the superior colliculus involving the reticulo-thalamic tracts and deep tegmental nuclei inhibited anaphylactic death. Szentivanyi and Filipp were among the first to study the role of the hypothalamus on anaphylaxis. They demonstrated that lethal anaphylactic shock in the guinea pig and the rabbit can be prevented by bilateral focal lesions in the tuberal region of the hypothalamus. Luparello, Stein, and Park investigated the effect of hypothalamic lesions on rat anaphylaxis and found that anterior, but not posterior, hypothalamic lesions inhibited development of lethal anaphylaxis in the rat. In a recent study reported by Macris, Schiavi, et al., it has been shown that lesions in the anterior hypothalamus of actively immunized guinea pigs afforded significant protection against lethal anaphylaxis. Lesions in the median and posterior basal hypothalamus did not modify anaphylactic reactions.

Little is known about the mechanisms involved in the antianaphylactic effect of hypothalamic lesions. Filipp and Szentivanyi have reported that circulating as well as tissue-fixed antibodies were markedly reduced in

guinea pigs injured in the tuberal region. Low precipitin levels were observed in sensitized animals following hypothalamic lesions as evidenced by the Ring test. Korneva and Khai also found that lesions in the posterior ventral hypothalamus of rabbits completely suppressed the production of complement-fixing antibodies and induced a prolonged retention of the antigen in the blood. In cases where the areas of destruction were localized in other parts of the hypothalamus, the thalamic structure, the caudate nucleus, and the posterior commissure, the course of immune processes was similar to that in control animals. It has been found that anterior hypothalamic lesions in the guinea pig were associated with significantly lower circulating antibody titers.

The significance of the low-circulating antibodies in the decreased anaphylactic response remains to be determined. If the antianaphylactic effect was due solely to diminished antibody production, then no protection would be expected in animals passively immunized with antibody levels that are sufficient to produce lethal anaphylaxis. Szentivanyi and Filipp have reported that guinea pigs passively sensitized with homologous as well as with heterologous (rabbit) serum are protected by hypothalamic lesions. These investigators did not identify the hypothalamic structures damaged by the lesions nor did they quantify the amount of antibodies injected to the animals. Macris, Schiavi, et al. investigated the effect of hypothalamic lesions in guinea pigs passively immunized with heterologous (rabbit)

antiovalbumin. Significant protection against passive lethal anaphylaxis was found in the animals with anterior but not with posterior hypothalamic lesions.

There are several mechanisms that may be involved in the protective action of anterior hypothalamic lesions in addition to their effect on circulating antibodies. The lesions may interfere with antibody binding to host tissues; they may alter the content and release of histamine and other mediator substances by the tissues; or they may diminish the responsiveness of the target tissue to the pharmacological agents liberated by the antigen-antibody reaction. Several studies have reported that the CNS modified the susceptibility of animals to histamine which, in the guinea pig, is the main agent responsible for the acute anaphylactic reaction. Whittier and Orr found that bilateral lesions of the caudate nuclei of rats were associated with a significant increase in survival time following the intraperitoneal administration of histamine phosphate; sham operations and lesions in the cerebral cortex did not modify the time of survival. Przbylski investigated the effect of the removal of the region of quadrigeminal bodies and of the cerebral cortex on histamine toxicity in guinea pigs. The animals in which the quadrigeminal bodies were removed showed a decreased susceptibility to histamine when administered either intravenously or by the inhalation of an aerosol. Removal of the cerebral cortex did not modify the reactivity of the animals.

Schiavi, Adams, and Stein studied the effect of bilateral electrolytic lesions in the anterior and posterior medial hypothalamus of guinea pigs on histamine toxicity as measured by dose-mortality curves and the LD50. The animals with anterior lesions were afforded significant protection against histamine toxicity. The mechanism by which anterior hypothalamic lesions modifies the susceptibility of the animals to exogenous histamine is not apparent from this study. Maslinski and Karczewski extensively investigated the effect of electrical stimulation of the brain of guinea pigs with current intensities above and below the seizure threshold on the susceptibility of the animals to histamine. They found that electrical stimulation of guinea pigs through temporal electrodes with a 50-100 Hz. current at levels between 8 and 10 milli amp. has a marked protective effect against lethal histamine shock. These investigators demonstrated that the decrease in histamine susceptibility was transitory and was associated with a marked decrease in the bronchospastic effect of histamine. Karczewski found that the parameters of electrical stimulation effective against lethal histamine shock also induced a marked depression of the electrical activity of the afferent and efferent fibers of the vagus. This and other observations led him to postulate that the modified histamine susceptibility following brain stimulation could be due to a reduced physiological tone of the airways leading to a reduced response to the constricting stimuli. A study by Mills and Widdicombe conducted on vagotomized guinea pigs provided evidence that a vagal reflex is partially

responsible for the bronchoconstriction occurring in anaphylaxis and following intravenous administration of histamine. A decreased response to broncho-constricting agents due to an autonomic imbalance induced by the anterior hypothalamic lesions deserves further consideration.

Extensive work has demonstrated that the hypothalamus is intimately involved with autonomic nervous activity. Several lines of evidence indicate that bronchomotor tone is the result of a balance between parasympathetic and sympathetic influences. Damage to the region of the anterior hypothalamus, which is thought to mediate primarily parasympathetic responses may decrease vagal bronchoconstrictor tone resulting in the predominance of bronchial adrenergic β-receptor activity. In keeping with this hypothesis, inhibition of vagal activity or β-adrenergic stimulation decrease histamine induced bronchoconstriction while blockage of β-receptors potentiate histamine broncho-spasm.

Szentivanyi has postulated that the hyperreactivity observed in bronchial asthma may be due to the reduced functioning of the β-adrenergic system leading to α-adrenergic dominance and the consequent increase in bronchial responsiveness to the various pharmacological mediators. Orange and Austen have reported that increased intracellular levels of cyclic adenosine-3'5'-mono-phosphate (cyclic AMP) following activation of β-adrenergic receptors inhibit the IgE mediated immunological release of

histamine and “slow reactive substance” (SRS-A) from lung tissues. Hypothalamic lesions may produce a functional imbalance in the two adrenergic effector systems or increase the levels of cyclic AMP resulting in an inhibition of release of histamine and SRS-A; at present, however, there are no data to support these possibilities.

The influence of the CNS on immune mechanisms may be due, at least in part, to changes in neuroendocrine function induced by the destruction of specific hypothalamic structures. It has been shown in the rat that the anterior medial hypothalamus is involved in the regulation of the secretion of thyroid stimulating hormone (TSH) by the hypophysis. Electrolytic lesions in this area induce low plasma levels of TSH and decreased thyroid function. A number of investigators have demonstrated in the rat and guinea pig a relationship between thyroid physiology and immune processes. It has been noted that the resistance to the anaphylactic reaction is increased in thyroidectomized rats. Similar findings were observed by Nilzen in the guinea pig following thyroidectomy or administration of I. Suppression of thyroid activity inhibits local and systemic anaphylaxis, abolishes circulating precipitins, and decreases the susceptibility of the animals to exogenous histamine. Little is known about the effect of anterior hypothalamic lesions on thyroid function in the guinea pig.

Hypothalamic lesions can also modify ACTH secretion and blood

corticoid levels. Adrenal steroids have been found to have a protective effect against anaphylactic shock in the rat and an inhibitory effect on antibody formation in rats and guinea pigs. Adrenocortical hormones (ACTH) also have a profound action on the metabolism and effects of histamine. They have inhibitory effects on histamine decarboxylase activity, tissue binding of newly formed histamine and on the amount of histamine released by the tissues. Although adrenal steroids have a protective effect against histamine toxicity in mice and rats, they do not appear to modify significantly the susceptibility of guinea pigs to anaphylaxis and to exogenous histamine.

It has been suggested that the protective effect of anterior lesions may also be due to simultaneous changes in thyroid and adrenocortical function. Filipp and Mess reported that exogenous administration of thyroxin partially restored the sensitivity to anaphylaxis of actively immunized guinea pigs with lesions in the tuberal area of the hypothalamus. In another study the same authors investigated the combined effect of thyroxin and metopirone, an inhibitor of adrenocorticol hormone synthesis, on the anaphylactic response of sensitized guinea pigs with lesions in the tuberal region. The observation that the administration of both substances completely abolished the protective effect of the lesions led the investigators to postulate that the anti-anaphylactic effect of hypothalamic damage is due to the combined effect of decreased thyroid function and increased adrenocortical activity. There have been very few studies concerned with the neuroendocrine effects of localized

hypothalamic damage in guinea pigs. Additional information is necessary on plasma levels of thyroid, adrenocortical, and adrenomedullary hormones in guinea pigs with well defined hypothalamic lesions effective in decreasing anaphylactic reactivity.

Concluding Remarks

This chapter has reviewed the effect of psychosocial influences on infectious diseases, allergic disorders, autoimmune diseases, organ transplantation, and cancer. Clinical and experimental data have been presented which suggest that the effect of psychosocial factors on these disorders is due at least in part to an alteration in immunological mechanisms. The role of the CNS in relation to immune processes has also been discussed. The complexity of the psychophysiological processes involved in the role of psychosocial factors on immune disorders has been emphasized.

Bibliography

Abramoff, P. and M. LaVia. *Biology of the Immune Response.* New York: McGraw-Hill, 1970.

Ader, R. and S. B. Friedman. "Differential Early Experiences and Susceptibility to Transplanted Tumor in the Rat," *J. Comp. Physiol. Psychol.,* 59 (1965), 361-364.

Aviado, D. M. "Antiasthmatic Action of Sympathomimetics: A Review of the Literature on Their Bronchopulmonary Effects," *J. Clin. Pharmacol.,* 10 (1970), 217-221.

Bahnson, C. B. "Second Conference on Psychophysiological Aspects of Cancer," *Ann. N.Y. Acad. Sci.,* 164 (1969), 307-634.

Bahnson, C. B. and M. B. Bahnson. "Role of the Ego Defenses: Denial and Repression in the Etiology of Malignant Neoplasia," *Ann. N.Y. Acad. Sci.,* 125 (1966), 827-845.

Basch, S. H. "The Intrapsychic Integration of a New Organ: A Clinical Study of Kidney Transplantation," *Psychoanal. Q.,* 42 (1973), 364-384.

Berenbaum, M. C. "Effects of Carcinogens on Immune Processes," *Br. Med. Bull.,* 20 (1964), 159-164.

Black, S., J. H. Humphrey, and J. S. F. Niven. "Inhibition of Mantoux Reaction by Direct Suggestion under Hypnosis," *Br. Med. J.,* 1 (1963), 1649-1652. g. Block, J. "Further Consideration of Psychosomatic Predisposing Factors in Allergy," *Psychosom. Med.,* 30 (1968), 202-208.

Bock, E., B. Weeke, and O. J. Rafaelsen. "Serum Proteins in Acutely Psychotic Patients," *J. Psychiatr. Res.,* 9 (1971), 1-9.

Bogendorfer, L. "Uber den Einfluss des Zentralnervensystems auf Immunitatsvor-gange: Beziehungen des Sympathicus zum Zustandekommen der Agglutination," *Arch. Exp. Pathol. Pharmakol.,* 133 (1928), 107-no.

Burnet, F. M. *The Clonal Selection Theory of Acquired Immunity.* Nashville, Tenn.: Vanderbilt University Press, 1959.

Burnet, F. M. and F. Fenner. *The Production of Antibodies.* Melbourne: McMillan, 1941.

Castelnuovo-Tedesco, P., ed. *Psychiatric Aspects of Organ Transplantation.* New York: Grune & Stratton, 1971.

Chang, S. S. and A. F. Rasmussen. "Stress-Induced Suppression of Interferon Production in Virus Infected Mice," *Nature,* 205 (1965), 623-624.

Cooper, I. S. "Neurological Evaluation of Cutaneous Histamine Reaction," *J. Clin. Invest.,* 29 (1950),

465-469.

Crisp, A. H. "Some Psychosomatic Aspects of Neoplasia," *Br. J. Med. Psychol.,* 13 (1970), 313-331.

DeJong, W. and J. Moll. "Differential Effects of Hypothalamic Lesions on Pituitary-Thyroid Activity in the Rat," *Acta Endocrinol. (Kbh.)*, 48 (1965), 522-535.

Dews, P. B. and C. F. Code. "Effect of Cortisone on Anaphylactic Shock in Adrenalectomized Rats," *J. Pharmacol. Exp. Therap.,* 101 (1951), 9.

----. "Anaphylactic Reactions and Concentrations of Antibodies in Rats and Rabbits. Effect of Adrenalectomy and of Administration of Cortisone," *J. Immunol.,* 70 (1953), 199-206.

Dzhumkhade, A. P. "Role of Conditioned Reflexes in Production of Antibodies," *Zh. Vyssh. Nerv. Deiat.,* 10 (1960), 599-601.

Ebresen, P. and R. Rask-Nielsen. "Influence of Sex-Segregated Grouping and of Inoculation with Subcellular Leukemic Material on Development of Non-Leukemic Lesions in DBA/2, BALB/C and CBA Mice," *J. Natl. Cancer Inst.,* 39 (1967), 917-925'

Eisendrath, R. M. "The Role of Grief and Fear in the Death of Kidney Transplant Patients," *Am. J. Psychiatry,* 126 (1969), 129-135.

Filipp, G. and B. Mess. "Role of the Thyroid Hormone System in Suppression of Anaphylaxis Due to Electrolytic Lesion of the Tuberal Region of the Hypothalamus," *Ann. Allergy,* 27 (1969), 500-505.

----. "Role of the Adrenocortical System in Suppressing Anaphylaxis after Hypothalamic Lesion," *Ann. Allergy,* 27 (1969), 607-610.

Filipp, G. and A. Szentivanyi. "Anaphylaxis and the Nervous System, Part III," *Ann. Allergy,* 16 (1958), 306-311.

Fisherman, E. "Does the Allergic Diathesis Influence Malignancy?" *J. Allergy,* 31 (1960), 74-78.

Florsheim, W. H. "The Effect of Anterior Hypothalamic Lesions on Thyroid Function and Goiter Development in the Rat," *Endocrinol.,* 62 (1958), 783-789.

Freedman, D. X. and G. Fenichel. "Effect of Midbrain Lesions on Experimental Allergy," *Arch. Neurol. Psychiatry,* 79 (1958), 164-169.

Freeman, E. H., B. F. Feingold, K. Schlesinger et al. "Psychological Variables in Allergic Disorders: A Review," *Psychosom. Med.,* 26 (1964), 543-575.

Freeman, E. H., F. J. Gorman, M. T. Singer et al. "Personality Variables and Allergic Skin Reactivity," *Psychosom. Med.,* 29 (1967), 312-322.

Friedman, S. B. and L. A. Glasgow. "Psychologic Factors and Resistance to Infectious Disease," *Pediatr. Clin. North Am.,* 13 (1966), 315-335.

Friedman, S. B., L. A. Glasgow, and R. Ader. "Psychosocial Factors Modifying Host Resistance to Experimental Infections," in C. B. Balmson, ed., *Second Conference on Psychophysiological Aspects of Cancer. Ann. N.Y. Acad. Sci.,* 164 (1969), 381-393.

Fudenberg, H. H. "Immunologic Deficiency, Lymphoma and Autoimmune Diseases: Observations, Implications, Speculations," *Arthritis Rheum.,* 9 (1966), 464-472.

----. "Are Autoimmune Diseases Immunologic Deficiency States?" in R. A. Good and D. W. Fisher, eds., *Immunobiology,* PP-175-183. Stamford, Conn.: Sinauer Associates, 1971.

Gellhorn, E. *Autonomic Imbalance and the Hypothalamus.* Minneapolis: University of Minnesota Press, 1957.

Gellhorn, E., H. Nakao, and E. S. Regate. "The Influence of Lesions in the Anterior and Posterior Hypothalamus on Tonic and Phasic Autonomic Reactions," *J. Physiol.,* 131 (1956), 402-423.

Geocaris, K. "Circumoral Herpes Simplex and Separation Experiences in Psychotherapy," *Psychosom. Med.,* 23 (1961), 41-47.

Gold, E. R. and D. B. Peacock. *Basic Immunology.* Bristol, England: John Wright, 1970.

Greenfield, N. S., R. Roessler, and A. P. Crosley. "Ego Strength and Length of Recovery from Infectious Mononucleosis," *J. Nerv. Ment. Dis.,* 128 (1959), 125-128.

Hagnell, O. "The Premorbid Personality of Persons Who Develop Cancer in a Total Population Investigated in 1947 and 1957," *Ann. N.Y. Acad. Sci.,* 125 (1966), 846-855.

Hasek, M., A. Lengerova, and T. Hraba. "Transplantation Immunity and Tolerance," *Adv. Immunol.,* 1 (1961), 1-56.

Hawkins, N. G., R. Davies, and T. H. Holmes. "Evidence of Psychosocial Factors in the Development of Pulmonary Tuberculosis," *Am. Rev. Tuberc. Pulmon. Dis.,* 75 (1957), 5-10.

Herxheimer, H. "Bronchoconstrictor Agents and Their Antagonists in the Intact Guinea Pig," *Arch. Int. Pharmacodyn. Ther.,* 106 (1956), 371-380.

Hicks, R. "The Effects of Drug-Induced Adrenocortical Deficiency and of Mineralocorticoid Drugs on Anaphylaxis in the Guinea Pig," *J. Pharm. Pharmacol.,* 20 (1968), 497-504.

Hill, C. W., W. E. Greer, and O. Felsenfeld. "Psychological Stress, Early Response to Foreign Protein and Blood Cortisol in Vervets," *Psychosom. Med.,* 29 (1967), 279-283.

Holmes, T. H., T. Treuting, and H. G. Wolff. "Life Situations, Emotions and Nasal Disease," *Psychosom. Med.,* 13 (1951). 71-82.

Hume, D. M. "Immunological Consequences of Organ Homotransplantation in Man," *Harvey Led.,* 64 (1968-1969), 261-388.

----. "Organ Transplants and Immunity," in R. A. Good and D. W. Fisher, eds., *Immunobiology,* pp. 185-194. Stamford, Conn.: Sinauer Associates, 1971.

Imboden, J. B., A. Carter, and E. C. Leighton. "Convalescence from Influenza: A Study of the Psychological and Clinical Determinants," *Arch. Intern. Med.,* 108 (1961), 115-123.

Jacobs, M. A., L. S. Anderson, H. D. Eisman et al. "Interaction of Psychologic and Biologic Predisposing Factors in Allergic Disorders," *Psychosom. Med.,* 29 (1967), 572-585.

Jensen, M. M., and A. F. Rasmussen, Jr. “Stress and Susceptibility to Viral Infections: II. Sound Stress and Susceptibility to Vesicular Stomatitis Virus,” *J. Immunol.,* 90 (1963), 21-23.

Johnson, T., J. F. Lavender, E. Hullin et al. “The Influence of Avoidance-Learning Stress on Resistance to Coxsackie B. Virus in Mice,” *J. Immunol.,* 91 (1963), 569-575.

Johnson, T. and A. F. Rasmussen, Jr. “Emotional Stress and Susceptibility to Poliomyelitis Virus Infection in Mice,” *Arch. Gesamte Virusforsch.,* 18 (1965), 392-398.

Karczewski, W. “The Electrical Activity of the Vagus Nerve After an ‘Antianaphylactic’ Stimulation of the Brain,” *Ada. Allergol. (Kbh)*, 19 (1964), 229-235.

Karczewski, W., P. S. Richardson, and J. G. Widdicombe . “The Role of the Vagus Nerves in Determining Total Lung Resistance and Histamine-Induced Bronchoconstriction in Rabbits,” *J. Physiol.,* 181 (1965), 20P.

Kass, E. H. “Hormones and Host Resistance to Infection,” *Baderiol. Rev.,* 24 (1960), 177-185.

Kemph, J. P. “Renal Failure, Artificial Kidney and Kidney Transplant,” *Am. J. Psychiatry,* 122 (1966), 1270-1274.

Kissen, D. M. “Relationship between Lung Cancer, Cigarette Smoking, Inhalation, and Personality,” *Br. J. Med. Psychol.,* 37 (1964), 203-216.

----. “Psychosocial Factors, Personality and Lung Cancer in Men Aged 55-64,” *Br. J. Med. Psychol.,* 40 (1967), 29-43.

Kissen, D. M. and L. L. LeShan, eds. *Psychosomatic Aspeds of Neoplastic Disease.* London: Pitman, 1964.

Knapp, P. H. and S. J. Nemetz. “Acute Bronchial Asthma: I. Concomitant Depression and Excitement and Varied Antecedent Patterns in 406 Attacks,” *Psychosom. Med.,* 22 (1960), 42-56.

Korneva, E. A. and L. M. Khai. “Effect of Destruction of Hypothalamic Areas on Immunogenesis,”

Fed. Proc. Transl. Suppl.), 23 (1964), T88-92.

Leger, J. and G. Masson. "Factors Influencing an Anaphylactoid Reaction in the Rat," *Fed. Proc.,* 6 (1947), 150-151.

LeShan, L. L. "An Emotional Life-History Pattern Associated with Neoplastic Disease," *Ann. N.Y. Acad. Sci.,* 125 (1966), 780-793.

Levine, S. and C. Cohen. "Differential Survival to Leukemia as a Function of Infantile Stimulation in DB A/Z Mice," *Proc. Soc. Exp. Biol. Med.,* 102 (1959), 53-54.

Lukyanenko, V. L. "The Conditioned Reflex Regulation of Immunological Reactions," *Zh. Mikrobiol. Epidemiol. Immunobiol.,* 30 (1959). 53-59.

Luparello, T. J., M. Stein, and D. C. Park. "Effect of Hypothalamic Lesions on Rat Anaphylaxis," *Am. J. Physiol.,* 207 (1964), 911-914.

McClary, A. R., E. Meyer, and D. J. Weitzman. "Observations on the Role of Mechanism of Depression in Some Patients with Disseminated Lupus Erythermatosus," *Psychosom. Med.,* 17 (1955), 311-321.

McCulloch, M. W., C. Proctor, and M. J. Rand. "Evidence for an Adrenergic Homeostatic Bronchodilator Reflex Mechanism," *Europ. J. Pharmacol.,* 2 (1967), 214-223.

McFadden, E. R., Jr., T. Luparello, H. A. Lyons et al. "The Mechanism of Action of Suggestion in the Induction of Acute Asthma Attacks," *Psychosom. Med.,* 31 (1969), 134-143.

Macris, N. T., R. C. Schiavi, M. D. Camerino et al. "Effect of Hypothalamic Lesions on Immune Processes in the Guinea Pig," *Am. J. Physiol.,* 219 (1970), 1205-1209.

----. "Effect of Hypothalamic Lesions on Passive Anaphylaxis in the Guinea Pig," *Am. J. Physiol.,* 222 (1972), 1054-1057.

Marchant, J. "The Effects of Different Social Conditions on Breast Cancer Induction in Three Genetic Types of Mice by Dibenz (A,H) Anthracene and a Comparison with Breast Carcinogenesis by 3-Methylcholanthrene," *Br. J. Cancer,* 21 (1967), 576-585.

Marsh, J. T., J. F. Lavender, S. S. Chang et al. “Poliomyelitis in Monkeys: Decreased Susceptibility after Avoidance Stress,” *Science,* 140 (1963), 1414-1415.

Marsh, J. T. and A. F. Rasmussen, Jr. “Response of Adrenal, Thymus, Spleen and Leucocytes to Shuttle Box and Confinement Stress,” *Proc. Soc. Exp. Biol. Med.,* 104 (1960), 180-183.

Maslinski, C. and W. Karczewski. “Prevention of So-Called Histamine Shock by Stimulation of the Brain with Electric Current: Preliminary Communication,” *Acta. Physiol. Pol.,* 6 (1955), 372-376.

----. “The Protective Influences of Brain Stimulation by Electric Current on Histamine Shock in Guinea Pigs,” *Bull. Acad. Pol. Sci.,* 5 (1957), 57-62.

Meyer, R. J. and R. J. Haggerty. “Streptococcal Infections in Families: Factors Altering Individual Susceptibility,” *Pediatrics,* 29 (1962), 539-549.

Miescher, P. A. and H. J. Muller-Eberhard, eds. *Textbook of Immunolopathology.* New York: Grune & Stratton, 1968.

Mills, J. E. and J. G. Widdicombe. “Role of the Vagus Nerves in Anaphylaxis and Histamine-Induced Bronchoconstrictions in Guinea Pigs,” *Br. J. Pharmacol.,* 39 (1970), 724-731.

Moos, R. H. “Personality Factors Associated with Rheumatoid Arthritis: A Review,” *J. Chronic Dis.,* 17 (1963), 41.

Moos, R. H. and G. F. Solomon. “Personality Correlates of the Rapidity of Progression of Rheumatoid Arthritis,” *Am. Rheum. Dis.,* 23 (1964), 145-151.

----. “Psychologic Comparisons between Women with Rheumatoid Arthritis and Their Non-Arthritic Sisters: I. Personality Test and Interview Rating Data,” *Psychosom. Med.,* 27 (1965), 135-149.

----. “Psychologic Comparisons between Women with Rheumatoid Arthritis and Their Non-Arthritic Sisters: II. Content Analysis of Interviews,” *Psychosom. Med.,* 27 (1965), 150-164.

----. "Personality Correlates of the Degree of Functional Incapacity of Patients with Physical Disease," *J. Chronic Dis.,* 18 (1965), 1019-1038.

Monaenkov, A. M. "The Influence of Changes in the Activity of the Cerebral Hemispheres in Immunological Reactions," *Zh. Mikrobiol. Epidemiol. Immunobiol.,* 12 (1956), 88-89.

Movat, H. Z. *Inflammation, Immunity and Hypersensitivity.* New York: Harper & Row, 1971.

Nilzen, A. "The Influence of the Thyroid Gland on Hypersensitivity Reactions in Animals: I," *Acta Allergol. (Kbh)*, 7 (1955), 231-234.

----. "The Influence of the Thyroid Gland on Hypersensitivity Reactions in Animals: II," *Acta Allergol. (Kbh),* 8 (1955). 57-60.

----. "The Influence of the Thyroid Gland on Hypersensitivity Reactions in Animals: III," *Acta Altergol. (Kbh)*, 8 (1955), 103-111.

Orange, R. P. and F. Austen. "Chemical Mediators of Immediate Hypersensitivity," in R. A. Good and D. W. Fisher, eds., *Immunobiology,* pp. 115-121. Stamford, Conn.: Sinauer Associates, 1971.

Otto, R. and I. P. Mackay. "Psychosocial and Emotional Disturbance in Systemic Lupus Erythematosus," *Med. J. Aust.,* 2 (1967), 488-491.

Parrot, J. L. and C. Laborde. "Inhibition d'histidine-decarboxylase par la cortisone et par le salicylate de sodium," *J. Physiol.,* 53 (1955), 441-442.

Petrovskii, I. N. "Problems of Nervous Control in Immunity Reactions: II. The Influence of Experimental Neurosis on Immunity Reactions," ZH. *Mikrobiol. Epidemiol. Immunobiol.,* 32 (1961), 1451-1458.

Porter, J. C. "Secretion of Corticosterone in Rats with Anterior Hypothalamic Lesions," *Am. J. Physiol.,* 204 (1963), 715-718.

Przbylski, A. "Effect of the Removal of Cortex Cerebri and the Quadrigeminal Bodies Region on Histamine Susceptibility of Guinea Pigs," *Acta. Physiol. Pol.,* 13 (1962), 535-541.

Rasmussen, A. F. Jr. “Emotions and Immunity,” in C. B. Bahnson, ed., *Second Conference on Psychophysiological Aspects of Cancer. Ann. N.Y. Acad. Sci.,* 164 (1969), 458-462.

Rasmussen, A. F. Jr., J. T. Marsh, and N. Q. Brill. “Increased Susceptibility to Herpes Simplex in Mice Subjected to Avoidance-Learning Stress or Restraint,” *Proc. Soc. Exp. Biol. Med.,* 96 (1957), 183-189.

Rasmussen, A. F., Jr., E. T. Spencer, and J. T. Marsh. “Decrease in Susceptibility of Mice to Passive Anaphylaxis Following Avoidance-Learning Stress,” *Proc. Soc. Exp. Biol. Med.,* 100 (1959), 878-879.

Rees, W. L. “Physical and Emotional Factors in Bronchial Asthma,” *J. Psychosom. Res.,* 1 (1956), 98-114.

----. “The Role of the Autonomic Nervous System in Asthma and Allied Disorders,” *J. Psychosom. Res.,* 9 (1965), 159-163.

Rose, B. “Hormones and Allergic Responses,” in J. H. Shaffer, G. A. LoGrippo, and M. W. Chase, eds., *International Symposium on Mechanisms of Hypersensitivity,* PP 599-634, London: Churchill, 1959.

Russell, P. S. and A. P. Monaco. “The Biology of Tissue Transplantation,” *N. Engl. J. Med.,* 271 (1964), 502, 553, 610, 664, 718, 776.

Rytel, M. W. and E. D. Kilbourne. “The Influence of Cortisone on Experimental Viral Infection,” *J. Exp. Med.,* 123 (1966), 767-775.

Salk, J. “Theoretical Psychophysiological Considerations,” in Bahnson, C. B., ed., Second Conference on Psychophysiological Aspects of Cancer. *Ann. N.Y. Acad. Sci.,* 164 (1969), 590-610.

Savchuk, O. Y. “The Reflex Mechanism of the Formation of Antibodies,” *Zh. Mikrobiol. Epidemiol. Immunobiol.,* 29 (1958), 123-131.

Schayer, R. W., J. K. Davis, and R. L. Smiley. “Binding of Histamine in Vitro and Its Inhibition by Cortisone,” *Am. J. Physiol.,* 182 (1955), 54-56.

Schiavi, R. C., J. Adams, and M. Stein. "Effect of Hypothalamic Lesions on Histamine Toxicity in the Guinea Pig," *Am. J. Physiol.,* 211 (1966), 1269-1273.

Schmale, A. H. and H. P. Iker. "The Affect of Hopelessness in the Development of Cancer: I. The Prediction of Uterine Cervical Cancer in Women with Atypical Cytology," *Psychosom. Med.,* 26 (1964), 634-635.

Schwartz, R. S. and Y. Borel. "Principles of Immunosuppressive Drug Action," in P. A. Miescher and H. J. Müller-Eberhard, eds., *Textbook of Immunopathology,* Vol. 1, pp. 227-235. New York: Grune & Stratton, 1968.

Solomon, G. F. "Stress and Antibody Response in Rats," *Arch. Allergy,* 35 (1969), 97-104.

----. "Emotion, Stress, the Central Nervous System and Immunity," in C. B. Bahnson, ed., *Second Conference on Psychophysiological Aspects of Cancer. Ann. N.Y. Acad. Sci.,* 164 (1969), 335-343.

----. "Psychophysiological Aspects of Rheumatoid Arthritis and Autoimmune Disease," in O. W. Hill, ed., *Modern Trends in Psychosomatic Medicine,* pp. 189-216. New York: Appleton-Century-Crofts, 1970.

Solomon, G. F., S. Levine, and J. K. Kraft. "Early Experience and Immunity," *Nature,* 220 (1968), 821-822.

Solomon, G. F., T. Merigan, and S. Levine. "Variation in Adrenal Cortical Hormones within Physiological Ranges, Stress and Interferon Production in Mice," *Proc. Soc. Exp. Biol. Med.,.* 126 (1967), 74-79.

Solomon, G. F. and R. H. Moos. "Psychologic Aspects of Response to Treatment in Rheumatoid Arthritis," *Gen. Pract.,* 32 (1965), 113-115.

Stjernsward, J. "Age-Dependent Tumor Host Barrier and Effect of Carcinogen-Induced Immunodepression on Rejection of Isografted Methylcholanthrene-Induced Sarcoma Cells," *J. Natl. Cancer Inst.,* 37 (1966), 505-512.

Szentivanyi, A. "The Beta Adrenergic Theory of the Atopic Abnormality in Bronchial Asthma," *J.*

Allergy, 42 (1968), 203-232.

Szentivanyi, A. and G. Filipp. "Anaphylaxis and the Nervous System, Part II," *Ann. Allergy,* 16 (1958), 143-151.

Treadwell, P. E. and A. F. Rasmussen, Jr. "Role of the Adrenals in Stress-Induced Resistance to Anaphylactic Shock," *J. Immunol.,* 87 (1961), 492-497.

Turk, J. L. *Immunology in Clinical Medicine.* New York: Appleton-Century-Crofts, 1969.

Vessey, S. H. "Effects of Grouping on Levels of Circulating Antibodies in Mice," *Proc. Soc. Exp. Biol.,* 115 (1964), 252-255.

Wan, W. C. and M. Stein. "Effect of Vagal Stimulation on the Mechanical Properties of the Lungs in Guinea Pigs," *Psychosom. Med.,* 30 (1968), 846-852.

Weil-Malherbe, H. and S. I. Szara. *The Biochemistry of Functional and Experimental Psychoses.* Springfield, Ill.: Charles C. Thomas, 1971.

Whittier, J. R. and A. Orr. "Hyperkinesia and Other Physiologic Effects of Caudate Deficit in the Adult Albino Rat," *Neurology,* 12 (1962), 529-539.

Widdicombe, J. G. "Regulation of Tracheobronchial Smooth Muscle," *Physiol. Rev.,* 43 (1963), 1-37.

Wistar, R. T. and W. H. Hildermann. "Effect of Stress on Skin Transplantation Immunity in Mice," *Science,* 131 (1960), 159-160.

Wollcock, A. J., P. T. Macklem, J. C. Hogg et al. "Influence of Autonomic Nervous System on Airway Resistance and Elastic Recoil," *J. Appl. Physiol.,* 26 (1969), 814-818.

Wollcock, A. J., P. T. Macklem, J. C. Hogg et al. "Effect of Vagal Stimulation on Central and Peripheral Airways in Dogs," *J. Appl. Physiol.,* 26 (1969), 806-813.

Wyatt, R. J., B. A. Termini, and J. Davis. *Biochemical and Sleep Studies of Schizophrenia: A Review of the Literature*— 1960-1970. Schizophrenia Bulletin, Issue no. 4. Washington, D.C.: Natl. Clearinghouse for Mental Health Information, Fall 1971.

Yamada, A., M. Jensen, and A. F. Rasmussen, Jr. “Stress and Susceptibility to Viral Infections: III. Antibody Response and Viral Retention during Avoidance Learning Stress,” *Proc. Soc. Exp. Biol. Med.,* 116 (1964), 677-680.

Yamasaki, H. and T. Yamamoto. “Inhibitory Effect of Adrenal Glucocorticoids on Histamine Release,” *Jap. J. Pharmacol.,* 13 (1963), 223-224.