Annu. Rev. Pharmacol. Toxicol. 1990. 30:561–602

INTERACTIONS BETWEEN THE BRAIN AND THE IMMUNE SYSTEM

Robert Ader, David Felten, and Nicholas Cohen

Departments of Psychiatry, Neurobiology and Anatomy, and Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642

KEY WORDS: psychoneuroimmunology, brain, behavior and immunity, neuroendocrine-immune networks, autonomic nervous system & immunity, stress and immunity

INTRODUCTION

For reasons that are not entirely clear, the neurosciences and immunology evolved without seriously considering the possibility of interactions between these systems that could mutually influence their respective functions (1). Within the past 10 years, research concerned with the relationships among brain, behavior, and immunity has expanded rapidly. Experiments have reliably documented the effects of behavior on immune function and the existence of unsuspected connections between the nervous and immune systems. Our purpose here is to provide a brief and highly selected overview of some of the evidence that behavioral factors are capable of influencing immune function and to describe some of the neural and endocrine channels of communication that link the brain and the immune system. Although systematic research in psychoneuroimmunology is relatively new, the range of the phenomena that bear on brain-behavior-immune system interactions is quite broad. There is an old and continuing experimental and clinical literature suggesting that immune function can be altered by psychological means, and there are provocative data suggesting that affective states and personality characteristics are associated with differences in immune function. Strategically and practically, such studies are difficult to implement, and unequivocal evidence for such associations does not yet exist. A discussion of these areas

0362-1642/90/0415-0561$02.00

is beyond the scope of this review. The present review concentrates on the experimental as opposed to the clinical literature concerning the effects of behavior (including stress) in the modulation of immune responses, and the interactive relationships among neural, endocrine, and immune processes that could lead to an explanation of such phenomena and a greater appreciation and understanding of integrated processes of adaptation.

BEHAVIORAL INFLUENCES ON IMMUNE FUNCTION

Effects of Stress

Studies in humans have implicated psychosocial factors in the susceptibility to and/or recovery from several infectious, bacterial, allergic, autoimmune, and neoplastic diseases that, to a greater or lesser extent, involve alterations in immunologic defense mechanisms (e.g. 2–5). Experimental studies in animals indicate that the outcome of stressful stimulation depends upon the nature of the stressor and the pathophysiological process to which the organism is exposed. That is, the same stressor may have different effects on different disease processes and different stressors may exert different effects on a particular pathophysiologic process. Presumably, the ability to predict the outcome of studies of the pathophysiologic effects of stress depends upon a more complete understanding of the effects unconditionally elicited by potentially pathogenic stimulation and the acute and chronic psychophysiological effects (including the immunologic effects) of the stressful stimulation upon which these are superimposed. Although such studies document the effects of psychosocial factors on alterations in susceptibility to disease, they do not provide direct evidence that such effects are mediated by psychosocially induced alterations in immune function.

Recently, attention has been directed to quantifying the changes in immune function that result from different stressful circumstances. The death of a family member, for example, is rated high on scales of stressful life events and has been associated with depression and an increased morbidity and mortality in a variety of diseases (e.g. 6–8), many of which are presumed to involve immune defense mechanisms. Thus, changes in immune function may constitute an important link between psychosocial factors on the one hand and altered susceptibility to or progression of disease on the other. Though this chain of psychophysiological events has not yet been established, changes in some features of immunologic reactivity such as a reduced lymphoproliferative response to mitogenic stimulation (9, 10) and impaired natural killer (NK) cell activity (11) have been observed among the bereaved. Still other studies have documented changes in immune reactivity associated with the affective responses to other losses such as marital separation and divorce (12).

The relationship between bereavement and depression has been commented upon frequently in the psychiatric literature, and studies of the immune changes associated with depression are just beginning. Lymphocyte responses to mitogens are reduced in drug-free, hospitalized depressed patients (13). No such differences are evident in an ambulatory population of patients with major depressive disorder (14). As hypothesized, the discrepancy could be due to differences in the severity of the disorder and/or the age of the hospitalized and nonhospitalized patients. In general, the limited number of studies on the immunologic effects of depression have yielded an inconsistent pattern of results. Some investigators have observed a significant suppression of one or another parameter of immunity (13–18); others have not (14, 19–21). In addition to the parameter(s) of immune function measured, one needs to consider the age and sex of the patient; the nature of the depression (endogenous vs nonendogenous, dexamethasone suppressors or nonsuppressors); whether patients are experiencing acute depression or are in remission; the severity and/or duration of depression, which may be related to whether patients are hospitalized or ambulatory; whether patients are drug-free (and for how long); and/or the presence or absence (and kind) of therapy. The clinical significance of the changes in immunologic reactivity that accompany bereavement or depression remains a primary and, as yet, unresolved concern.

Of related interest and importance is the rapidly growing literature concerning the immunomodulating effects of psychotropic drugs (22)—drugs of abuse as well as those used for therapeutic purposes (e.g. in the treatment of depression). Not surprisingly, the immunologic effects of psychotropic agents depend upon the species, the in vitro or in vivo immune response studied, the dose and/or duration of drug treatment, and, in experimental studies, the timing of drug administration in relation to antigenic stimulation. Psychotropic drug action, like the effects of many other experimenal interventions, also depends on the psychophysiological state of the organism upon which it is superimposed. For example, haloperidol reduces antibody responses in normal mice but restores humoral immunity when given to stressed (i.e. crowded) animals (23).

While the death of a spouse is intuitively stressful, changes in immune function can be observed in humans using intuitively less severe, but nonetheless effective, naturally occurring stressful stimulation. Changes in immune function in response to impending examinations in medical students and to football games in football players (and even spectators) was reported by Farris in 1938 (24). The level of distress during examination periods is invariably greater than that during control periods, and the Glasers (12) have found transient impairments in several parameters of immune function in medical students at such times. Relative to a nonstressful baseline measurement,

examination periods are associated with a decrease in mitogen responsiveness, NK cell activity, percentage of helper T-lymphocytes, and interferon production by stimulated lymphocytes. In students who are seropositive for Epstein-Barr virus (EBV), there are elevated anti-EBV antibody titers, interpreted as a poorer cellular immune response control over the latent virus, during examination than control periods (25). The incidence of self-reported symptoms of infectious illness is also increased during examination periods (26). Personality tests have not yielded differences between the students who volunteered for these studies and their classmates, and other life changes that could have influenced immune responses were minor and did not correlate with the changes in immune function.

Separation experiences (i.e. losses) have also been studied in animals. In rodents, periodic interruptions of mother-litter interactions and/or early weaning decreases lymphocyte proliferation to mitogenic stimulation and reduces the plaque-forming response to subsequent challenge with sheep red blood cells (SRBC) (27, 28). Whether the immunologic effects of premature weaning—or extended maternal care (29)—are attributable to nutritional factors, temperature regulation, and/or maternally mediated modifications of neural or endocrine development or function remains to be determined.

Infant monkeys (and their mothers) respond to separation with a transient depression of in vitro mitogen responsiveness that, like the studies of bereavement in humans, does not appear to be related to plasma cortisol levels (30, 31). Separation of squirrel monkeys from their mothers results in several changes in immunologic reactivity; these include a decline in complement protein levels (an effector mechanism in humoral immune responses), macrophage function, and IgG antibody responses to immunization with a benign bacteriophage, the magnitude of one or another of the effects being a function of the psychosocial environment in which the animals were housed following separation (32, 33). It is of interest that rhesus macaque monkeys, which show essentially the same behavioral responses to separation from the mother but differ substantially from squirrel monkeys in their endocrine responses, showed no changes in immune function following separation.

In adult animals, a variety of behavioral manipulations interpreted as being stressful to the organism are capable of influencing a variety of immune responses in a variety of species. As noted in the case of disease susceptibility, a detailed examination of the literature would reveal that the effects of stress on immunologic reactivity depend upon the quality as well as the quantity of the stressful stimulation (e.g. 34–37) and the immunogenic stimulation (38), the temporal relationship between stressful stimulation and immunogenic stimulation (e.g. 39–41), the immune response (or compartment) under study (e.g. 37, 42–44) and several host factors. One compelling illustration is provided by the single study (45) in which restraint, heat, and

cold (all considered stressors) were found to exert differential effects on the induction and/or expression of delayed-type hypersensitivity (DTH) and contact sensitivity, two cell-mediated responses. Again, predicting the outcome of such experiments depends upon a more complete understanding of the interaction between the effects unconditionally elicited by immunogenic stimulation and the acute and chronic psychophysiologial effects of the stressful stimulation upon which these are superimposed.

From a behavioral perspective, the most sophisticated experimental paradigms involve noxious environmental circumstances that are predictable or unpredictable, escapable or inescapable, or avoidable or unavoidable, thus holding constant the physical and noxious elements of the stress while providing some animals with the ability to adapt to or control their environment. Acute and chronic imposition of such experimental paradigms have, thus far, yielded interesting but inconsistent immunologic effects. Preliminary results have suggested that escapable footshock prevents the suppression of splenic NK cell activity seen in animals subjected to inescapable shock (46) and that inescapable but not escapable footshock results in a suppression of mitogen-induced lymphoproliferation (47). These latter results, however, cannot be consistently reproduced (48). Other investigators (45) have reported alterations in immunologic reactivity among animals subjected to electric shock with and without a warning signal or in animals that were or were not able to avoid the noxious stimulation. The existence and direction of the differences was a function of the parameter of immune function being measured.

Neuroendocrine states provide the internal milieu within which immune responses occur. Stimulating animals during prenatal and early life, varying social interactions among adult animals, and exposing animals to environmental circumstances over which they have no control are among the psychological manipulations that induce neuroendocrine changes that are implicated in the modulation of immune responses. As discussed below, our knowledge of interactions between neuroendocrine and immune function under normal and stressful conditions, however, is incomplete. Glucocorticoids, for example, are usually immunosuppressive. It is generally assumed, therefore, that an elevation in adrenocortical steroids, the most common manifestation of the effects of stress, is responsible for the frequently observed suppression of immunologic reactivity associated with stress. There are numerous examples of stress-induced, adrenocortically mediated alterations of immune responses, particularly in vitro; yet several other observations of stress-induced alterations in immunologic reactivity are independent of adrenocortical activation (40, 42, 49–56). Consistent with the effects of adrenalectomy, hypophysectomy obviates the effects of stress on some measures of immunity (numbers of peripheral blood and splenic leukocytes), but the stress-induced suppression of mitogen responsivity of peripheral blood lymphocytes is po-

tentiated by hypophysectomy (57). It seems evident that the in vivo immunologic consequences of stress involve extremely complex neural, endocrine, and immune response interactions. Considering that the elicitation of immune responses is itself capable of altering levels of circulating hormones and neurotransmitters, these interactions are also likely to include complex feedback and feedforward mechanisms.

Conditioned Alterations of Immunologic Reactivity

Learning, the most complex of all brain functions, is the primary means by which higher organisms adapt to their environment. A dramatic and compelling illustration of the role of the nervous system in the modulation of immunity, then, comes from several demonstrations that immune responses can be modified by conditioning. In the earliest studies of conditioning (e.g. 58, 59), a neutral conditioned stimulus (CS) was paired with injections of antigen and presentation of the CS alone was eventually able to elicit conditioned increases in nonspecific inflammatory responses and, in some cases, increases in antibody levels as well. These experiments and the ensuing controversy about their interpretation have been reviewed elsewhere (60).

Modern studies of conditioned alterations of immune responses began with a study by Ader & Cohen (61) who used a taste-aversion learning paradigm. In this passive avoidance situation, consumption of a novel, distinctively flavored drinking solution, the CS, is paired with a stimulus that causes some noxious internal effects, the unconditioned stimulus (UCS). For example, rats injected with cyclophosphamide (or any number of other drugs) after consuming saccharin-flavored water learn in a single trial to avoid drinking saccharin-flavored water. Using rats, consumption of saccharin-flavored water was paired with an intraperitoneal injection of the immunosuppresive drug, cyclophosphamide (CY). Three days later, all animals were immunized with SRBC and conditioned animals were randomly divided into three groups: Group CS was reexposed to the saccharin solution previously paired with the immunosuppressive drug and injected with saline; Group CSo, a control for the effects of conditioning per se, was provided with plain water and was not otherwise manipulated; and Group UCS was given plain water but injected with CY to define the unconditioned immunosuppressive effects of the drug. A nonconditioned group originally received CY without exposure to saccharin but, following immunization, was provided with a saccharin solution whenever any subsample of Group CS was reexposed to saccharin. A placebo group was originally injected with saline following the consumption of plain water.

As expected, the pairing of saccharin consumption with an injection of CY produced an aversion to saccharin-flavored water and, as hypothesized, con-

ditioned animals reexposed to the CS showed an attenuated antibody response to SRBC compared to nonconditioned animals and conditioned animals that were not reexposed to the CS. These data, and verification of the results by other investigators (62, 63), have been taken as evidence of a behaviorally conditioned suppression of immunologic reactivity. In one or another of such studies, the acquisition and extinction of the conditioned suppression or enhancement of antibody- and cell-mediated immune responses as well as nonspecific host-defense reactions has been documented using different CSs, different UCSs, different antigens, and different outcome measures. Extending this research, conditioning processes have been implicated in the development of tolerance to an immunomodulating agent (64, 65), the biologic effects of conditioned immunosuppressive responses have been elaborated in altering the progression of autoimmune disease in lupus-prone mice (66, 67) and mortality to a transplanted plasmacytoma (68), and conditioned increases in a specific mediator of mucosal mast cell function has been demonstrated (69). Most of this research has adopted a taste-aversion conditioning paradigm in which an immunomodulating drug has served as the UCS. It is now clear, however, that the phenomenon is not confined to conditioned immunopharmacologic responses. The immunologic effects of stress have been conditioned (e.g. 70) and conditioning effects have been observed using antigens as unconditioned stimuli (69, 71).

Compensatory responses characterize many (but not all) conditioned physiologic effects induced by drugs. One might therefore expect conditioned responses that are opposite in direction to the unconditioned effects of the immunopharmacologic drug used as the UCS. The data, however, are almost totally uniform in showing conditioned responses that mimic the unconditioned immunopharmacologic responses (63). Recent exceptions (72, 73) permit only the inference of compensatory mechanisms. The discrepancies raise methodological and mechanistic issues that need to be resolved. Another recurring issue concerns the prevalent use of aversive stimulus conditions, a limitation that also needs to be addressed. However, the notion that conditioned immune responses are inextricably linked with conditioned avoidance responses or that there is some direct relationship between conditioned behavioral and immunologic responses receives no support from the existing literature. To the extent that the sampling of different parameters of immune function under different experimental conditions is sufficiently representative, taste aversions can be expressed without concomitant changes in immune function, and conditioned changes in immune function can be obtained without observable conditioned avoidance responses (63). Consistent with the relationship between conditioned behavioral and autonomic or endocrine responses, the available data suggest that different (multiple) con-

ditioning processes and mechanisms are involved in the conditioning of behavioral and immune responses.

The physiologic mediation of conditioned alterations in immune function are not yet known. Some writers, however, have explicitly or implicitly assumed that the conditioned suppression of immunologic reactivity is a stress-induced effect. Since glucocorticoid elevations, equated with or taken as an index of stress, can suppress immune responses, the hypothesis is attractive because it provides a ready "explanation" of an unexplained phenomenon. The available data, however, provide no support for stress-induced elevations in "stress hormones," notably adrenocortical steroids, as the mediator of conditioned alterations in immune function. Indeed, much of the data stand in direct contradiction to such a hypothesis. There are problems in interpreting extirpation experiments, but is should be noted that, in one study (74), immunosuppression was not observed in adrenalectomized mice. However, the "stress-mediation" hypothesis cannot account for the following observations: no conditioned suppression of antibody production is observed when LiCl is used as the UCS or when steroid levels are elevated by injections of LiCl or corticosterone at the time of immunization (61, 75); conditioned suppression and/or enhancement of antibody- and/or cell-mediated responses occur in the presumed absence of, or with equivalent changes in, corticosterone and, presumably, other stress hormone levels (71, 76–78); in a preference-testing procedure that equates fluid consumption and obviates the conflict that occurs when animals are only exposed to the CS solution, conditioned immunosuppression is observed in the antibody response to T-dependent and T-independent antigens (76, 79), a graft-vs-host reaction (78), and in the white blood cell response to cyclophosphamide (80); and in a discriminative conditioning paradigm, both the CS+ and the CS− induce steroid elevations, but only the CS+ induces a conditioned release of histamine (81). It is reasonable to suggest that conditioned alterations of immunologic reactivity may be mediated by *conditioned* neuroendocrine responses, but the data collected thus far are inconsistent with the hypothesis that such effects are mediated simply by nonspecific, stress-induced changes in hormone levels.

The mechanisms underlying the conditioned modulation of immunity are not known, but there is no shortage of potential mediators and it is highly unlikely that multiple processes are involved. Conditioned immunosuppressive responses occur when conditioned animals are reexposed to the CS before as well as after immunization. Such effects could imply that the mechanisms do not involve antigen-induced immunologic or neuroendocrine changes; they could also indicate that different mechanisms are involved when conditioning is superimposed on a resting or on an antigen-activated system. Also, different immunomodulating agents have different sites of

action and the same immunomodulating drug may have different effects on activated or nonactivated lymphocytes. As described below, we now know that the immune system is innervated, that leukocytes and neurons share certain neuropeptide/neurotransmitter receptors, that lymphocytes can produce several neuroendocrine factors, and that cells of the immune system and the nervous system can produce and respond to the same cytokines. Thus, conditioned changes in the pattern of increases or decreases of neural and/or endocrine activity that can be recognized by activated lymphocytes or, conversely, the effects of conditioning on the release of immune products capable of being recognized by the nervous system constitute potential pathways underlying the conditioned modulation of immune functions.

Immunologic Effects on Behavior

Just as reciprocal relationships exist between neural and immune functions and endocrine and immune functions, accumulating data suggest immunologic influences on behavior as well as behavioral influences on immune function. The behavioral effects of (early) viral infections, the cognitive and emotional sequelae of autoimmune disease, and the behavioral differences between normal mice and those with a genetic susceptibility to autoimmune disease are reviewed elsewhere (82–86).

Recent data further suggest that behavioral changes associated with immunologic dysfunctions may actually be adaptive in maintaining or restoring homeostasis within the immune system. Lupus-prone (NZBxNZW)F_1 mice do not acquire conditioned taste aversions in response to doses of CY that induce conditioned avoidance responses in healthy control (C57BL/6) mice (87). Similarly, Mrl-lpr/lpr mice with manifest symptoms of autoimmune disease (lymphadenopathy and elevated autoantibody titers) do not avoid flavored solutions paired with doses of CY that induce taste aversions in congenic (Mrl+/+) control mice (88). These differences in behavior are not the result of a learning deficit in the lupus-prone mice because there are no substrain differences prior to the development of symptoms of disease nor when a nonimmunosuppressive drug is used as the UCS. Mrl-lpr/lpr mice with symptoms of autoimmune disease also voluntarily consume more of a CY-laced flavored drinking solution than asymptomatic controls, and they drink sufficient amounts of the CY-laced solution to attenuate lymphadenopathy and anti-single-stranded DNA antibody titers (89). Although not previously described with respect to the immune system, these data are consistent with a large literature on the bchavioral regulation of physiological states (85). Whether the animal is responding to nonspecific, immunologically induced pathophysiological changes in one or another target organ or, consistent with the bidirectional pathways that link the CNS and immune system, the brain is capable of receiving and processing information emanating from

the (dysregulated) immune system directly, remains to be determined. To the extent that the brain is capable of acting on information provided by the immune system, behavioral processes appear to have the potential to serve an in vivo immunoregulatory function.

ENDOCRINE SYSTEM-IMMUNE SYSTEM INTERACTIONS

Even though productive interactions among subsets of T and B lymphocytes and accessory cells *can* result in the production of antibody and effect T cells in vitro, the neuroendocrine milieu in which these cells normally live, and the cell surface and/or cytoplasmic receptors for a diversity of hormones and neuropeptides they express (90–92), provide the opportunity for modulatory and interactive signals from outside what has been traditionally viewed as the immune system. This section highlights some of the extensive results indicating that hormones of the anterior pituitary and the adrenal gland are immunomodulatory; that lymphocytes and accessory cells receive neuroendocrine cues; and that products of the leukocyte components of the immune system can communicate with and modulate endocrine and nervous system responses (92–95). (For a discussion of the immunomodulatory roles of hormones produced by the posterior pituitary, the thyroid gland, the pineal, the gonads, and the thymus, see 96–100).

Anterior Pituitary Hormones

Early studies (101–103) reported that strains of pituitary-deficient dwarf mice display certain immunological abnormalities including involution of the thymus, cellular hypoplasia of the bone marrow and secondary lymphoid tissues, and depressed cell-mediated and humoral immunity. Some subsequent studies with hypophysectomized (hypox) mice supported the proposition of an interrelationship between the pituitary and immune function. These observations led to a plethora of studies to determine which of the many hormones produced by or stored in the pituitary, and which of the hypothalamic-releasing hormones, could modulate immunity.

Hormones produced by the anterior lobe of the pituitary (the adenohypophysis) can be grouped into three major classes according to their amino acid sequence homology. One group includes growth hormone (GH) and prolactin (PRL). Adrenocorticotropin (ACTH), alpha melanotropin, and beta lipotropin (LPH) form a second group of peptides derived from the precursor protein, proopiomelanocortin (POMC). LPH is the prohormone for the morphine-like peptides, the endorphins. The third group includes thyroid-stimulating hormone (TSH) and the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormones (FSH).

GROWTH HORMONE (GH) GH deficiencies have been associated with abnormal cellularity of the bone marrow and thymus, and depressed T-cell function (104, 105), NK activity (106), and antibody responses (107, 108; for reviews, see 101, 102, 109). Administration of GH to GH-deficient animals affords some degree of immune reconstitution (102).

GH also has immunological effects when administered to normal as well as to hypox animals, or added to cultures of leukocytes harvested from intact animals. For example, age-associated changes in immunocompetence [e.g. T-cell mitogen-induced proliferative responses and interleukin-2 (IL-2) synthesis] and the architecture of the thymus of rats have been reversed by grafting a pituitary tumor cell line that produces GH and PRL (102, 110). Interestingly, injection of high doses of ovine GH failed to restore thymic histology and IL-2 production in aged rats but, like the cell grafts, it did augment mitogen responsivity of lymphocytes (111). GH reproducibly augmented the in vitro proliferation of transformed and normal lymphocytes (112, 113) and increased activity of alloantigen-specific cytotoxic T cells from intact animals (114). Injection of hypox rats with GH effected marked increases (comparable to those induced by interferon gamma (INF γ)) in superanion production by resident peritoneal macrophages that had been stimulated with zymosan (102). Moreover, peripheral blood and purified alveolar macrophages have been activated in vitro by GH to produce superoxide anions that nonspecifically killed ingested bacteria (115, 116), an effect that was inhibited with a specific antibody to GH. That these latter observations were made with a highly purified population of macrophages supports the notion that GH exerts a direct effect on macrophages. As might be inferred, thymocytes, transformed and resting peripheral lymphocytes, and monocytes express high-affinity receptors for GH (102).

The CNS, other hormones, products of pathogens, and the immune system itself, all contribute to the impact of GH on immunity. For example, viruses (117) or bacterial endotoxin increase secretion of GH in humans (118). Macrophage-derived interleukin-1 (IL-1) can also augment the systemic release of GH (119). The impact of splenic and thymic lymphocyte-produced immunoreactive (ir-) GH (120) on the endocrine and immune systems is just beginning to be deciphered. Thymosin fraction V, a group of low molecular weight peptides extracted from bovine thymuses, causes pituitary cells to increase their secretion of GH and PRL (121). This has led to the concept of a feedback loop between the thymus and pituitary (102). The restoration of immunity in hypox rats can be antagonized by ACTH. Finally, there are recent findings that the immunomodulatory effects of brain lesions are also mediated, at least in part, by the pituitary gland (122, 123).

PROLACTIN (PRL) PRL is involved in immunological processes (124) as well as with mammalian reproduction and lactation. Nagy et al (125) inhibited

pituitary PRL secretion in rats with the dopamine receptor agonist, bromocriptine, and observed suppressed antibody and DTH responses. Bernton and colleagues (124, 126, 127) reported that hypoprolactinemia induced by two different mechanisms (bromocriptine or cysteamine HCL) was associated with a failure to effectively deal with a challenge of *Listeria monocytogenes;* a depressed lectin-induced mitogenesis of T and B cells that was independent of IL-2 production or IL-2 receptor expression; a suppressed T-cell-dependent activation of macrophages; and a suppressed microbially induced T-cell production of INF γ (124, 127). Exogenous PRL reversed these defects (124). In vivo, antibodies to PRL inhibited lymphocyte proliferation (128), and administration of exogenous PRL or dopamine antagonists (to stimulate endogenous PRL release) resulted in increased mitogenic responsivity of lymphocytes, increased DTH responses, and reversed the profound immunosuppression effected by cyclosporin (124, 129, 130).

In contrast to its in vivo effects, obvious effects of PRL on the proliferation or IL-2 production of lymphocytes growth in lactogen-free cell culture have not been seen (124). However, when such cultures were incubated with low concentrations of an antibody to pituitary PRL, DNA synthesis and cell proliferation was markedly inhibited (124, 128). This, plus the observations that the inhibitory activity of the antibody could be absorbed on a PRL-affinity column but could not be found in antisera directed against GH or other hormones (124), suggests that the cultured cells themselves were producing ir-PRL. This idea has been directly supported by observations that lectin-stimulated normal lymphocytes (117, 131), the murine EL4 thymoma, the CTLL-2 cytotoxic mouse T cell line (124), and a human myeloma cell line (132) each produce factors with PRL-like bioactivity and immunoreactivity. Indeed, an antiserum against PRL dramatically inhibited the growth of EL4 and CTLL cells (124).

The complexity underlying PRL-immune system interactions is just beginning to be appreciated. The interactions include the dopaminergic system and cells of the immune system itself. For example, not only do lymphocytes produce ir-PRL, but IL-1 stimulates the pituitary to inhibit PRL release in vitro (133) and in vivo (124). Morcover, PRL interacts with other products of the endocrine system. Circulating PRL negatively regulates its own releasing factor and vasoactive intestinal peptide (VIP) regulates PRL levels (124), as do the opioids (124, 130). Steroid hormones also affect circulating PRL in that its release is elevated by estrogens (134) and inhibited by glucocorticoids (135). Exogenous or endogenous elevation of PRL in mice whose cortisone was also elevated reversed some (e.g. mitogen responsivity), but not all (e.g. lymphoid tissue atrophy) of the immunosuppressive effects of this glucocorticoid (124). Thus, PRL may function to counter some of the suppressive effects of glucocorticoids. Since acute physical or behavioral stressors induce

a rapid rise in PRL concentrations (124), PRL, like ACTH and the catecholamines, is a stress hormone. Unlike ACTH, however, the stress-associated PRL increase is followed by decreased PRL secretion and then refractoriness to further stimulation with repetition of the stressor (124, 136).

ACTH AND THE ENDOGENOUS OPIOIDS, ENDORPHINS AND ENKEPHALINS ACTH and the endogenous opioid peptides, alpha, beta, and gamma endorphin, are generated by enzymatic processing of the POMC precursor molecule (137, 138). Beta endorphin is composed of 31 amino acids; alpha and gamma endorphin are comprised of the first 16 and 17 amino acids, respectively, that make up beta endorphin. All lobes of the pituitary gland, the adrenal medulla (137), macrophages (138), antigen- or mitogen-activated lymphocytes (92, 139), and T cell incubated with anti-CD3 antibody (140) produce endorphins. In addition, corticotropin releasing factor (CRF) indirectly induces B cells to produce beta endorphin, apparently by stimulating monocytes to produce IL-1 (140, 141).

Parenterally administered ACTH affects an increased output of glucocorticoids from the adrenals and is immunosuppressive in several systems (e.g. antibody titer, Arthus type and anaphylatic hypersensitivity, allograft rejection (142)). The increase in plasma cortisol associated with ACTH causes a decrease of the hypothalamic neuropeptide CRF, which, in turn, decreases ACTH secretion and brings circulating cortisol levels back to normal (the so-called hypothalamo-pituitary-adrenal axis). At least some of these and other in vivo immunomodulatory sequelae of exogenous ACTH are clearly attributable to the glucocorticoid products of the target adrenal gland (discussed below) rather than to a direct effort of the pituitary-derived ACTH on cells of the immune system. However, in cell-culture systems, ACTH suppresses antibody production (143), interferes with macrophage tumoricidal activity (144), modulates B-cell function (145), and suppresses INF γ production (146).

Endorphins (and enkephalins) can modify antigen-specific or mitogen-dependent in vitro proliferation of lymphocytes (147, 148), NK activity (149, 150), antibody responses (143, 151), INF γ production (152), and phagocyte chemotaxis (153). Whether such responses are depressed or increased may depend on the amino acid sequence binding to the relevant opioid or non-opioid receptor (154, 155), and/or on the stage of activation or differentiation of the particular lymphocyte that binds the endorphin in question (139). For example, alpha endorphin and ACTH inhibit (143), whereas beta endorphin either enhances (139, 151) or has no effect (143) on the primary anti-SRBC antibody response.

Several mechanisms have been proposed to explain how different endorphins modulate immune responses. Endorphins and ACTH may alter the

immunologically relevant receptors on the lymphocytes to which they bind (139). Indeed, Heijnen and colleagues (140) have demonstrated that beta endorphin and ACTH modulate the CD2 (SRBC receptor) and CD3 (part of the T-cell antigen receptor complex) epitopes on human peripheral blood T cells. A second mechanism may relate to the recent finding by Heijnen and colleagues (140) that incubation of PHA-stimulated T cells with gamma endorphin effects a total disappearance of IL-2 receptors on T cells. Finally, gamma endorphin can apparently bind preferentially to certain HLA class I antigens (156), suggesting an immunogenetic component of the effects of endorphins on immune responses.

The enkephalins (methionine-enkephalin or met-enk and leucine-enkephalin or leu-enk) are pentapeptides that originate from the precursor molecule, proenkephalin A (137, 138). Enkephalins bind to specific opioid receptors in brain tissue and on lymphocytes and are immunomodulatory with respect to antibody formation in vitro and in vivo; the numbers of peripheral blood leukocytes; the number of T cell SRBC rosettes; thymic weight, resistance to viral and tumor challenges; leukocyte migration; antibody-dependent cell-mediated cytotoxicity; and production of IL-2 and expression of the IL-2 receptor (143, 157, 158). The dose and nature of the enkephalin, the dose and route of antigen administered, and the timing of enkephalin administration relative to antigen all play a role in determining the direction and extent of the immunomodulation. It is noteworthy that since opioid peptides are rather quickly degraded in blood, the balance between their secretion and catabolism may be crucial to their effect on immune function.

Levels of endorphins and enkephalins are increased by behavioral states such as stress. Interestingly, in a paradigm that involved either intermittent (naloxone-sensitive or opioid-mediated) or continuous (naloxone-insensitive) footshock stress, enhancement of tumor growth was seen only when opioid-mediated intermittent stress (which also depressed NK cytotoxicity) was involved (159). In other words, all stressors need not involve the same mediators.

Glucocorticoid Hormones Produced by the Adrenal Gland

Following early demonstrations that glucocorticoids caused lymphoid involution and exerted clinically important anti-inflammatory and immunosuppressive effects, studies of the mode and site of action of these steroids grew exponentially as did an understanding of the complexity of the immune system (142). Some of the dose- and regimen-related effects of exogenous glucocorticoids in different species include growth retardation and wasting; lymphopenia; increased catabolism of immunoglobulins and an associated decreased concentration in serum; depression of antibody formation; inhibition of adjuvant effects of *Corynebacterium parvum* on IgM

antibody formation; prolongation of tolerance; inhibition of skin and renal allograft rejection; retarded DTH reactions; inhibition of contact sensitivity; inhibition of generation of cytotoxic effect cells; reduction of mixed leukocyte reactions; reduced generation of T helper cells; alteration in lymphocyte recirculation pathways; and depressed NK reactivity (142, 160–163).

Glucocorticoids exert equally profound and immunologically relevant in vivo and in vitro effects on monocytes and macrophages. These include a suppression of numbers of circulating monocytes; class II MHC antigen expression; phagocytosis and intracellular killing of certain microorganisms; cytokine production/secretion; cytotoxicity by interferon-treated macrophages; numbers of epidermal Langerhans cells; biosynthesis of some complement components; Fc receptor expression; chemotaxis; antigen presentation; and production of inflammatory mediators such as plasminogen activator, elastase, and collagenase (142, 163).

Many of these observations were derived from studies that involved the introduction of pharmacological rather than physiological concentrations of glucocorticoids. Evidence that these adrenal steroids really do play an important in vivo immunoregulatory (physiological) role comes from studies on stress and from recent experiments revealing the effects of glucocortoids on the activity of immunoregulatory cytokines. It has long been known that stress activates the hypothalamo-pituitary-adrenal axis and that the effects of stress are associated with some alterations of immune function. In addition, at least some forms of stress are associated with an altered susceptibility to infection and neoplastic disease. Despite the fact that the glucocorticoid-induced down-regulatory modulations of the immune system are extensive, it would be simplistic to attribute all immunological consequences of altered behavioral states (i.e. stress, life-event changes, conditioning) solely to increased adrenocortical steroids. At low concentrations, glucocorticoids exert stimulatory effects on certain immunologic responses; higher concentrations routinely appear inhibitory. Also, the effects of opioid peptides and catecholamines that are produced in the adrenal medulla are subject to hypothalamic and pituitary influences and are immunomodulatory. Finally, as noted above, stress-induced immunodepression has been observed in adrenalectomized as well as in intact animals (42).

Besedovsky and colleagues (164–166) have reported a transient elevation of serum corticosterone in mice and rats during the peak of the antibody response and following administration of soluble products of Con A-activated T cells. They have proposed (167) that the antigen-induced increase in glucocorticoids regulates overproduction of antibody and, as such, may explain the phenomenon of "antigenic competition" (the depressed primary antibody response to an antigen administered within a few days after the primary immunization of that animal with an unregulated antigen). Adre-

nalectomy partially abolished antigen competition (167) and was also associated with enhanced B-cell activity (168). These observations led to the hypothesis that the immune system itself can regulate the hypothalamo-pituitary-adrenal axis by means of cytokines released from activated monocytes (169). As discussed above, this idea has recently received significant support in that IL-1 stimulates secretion of hypothalamic CRH (95, 170) and increases the concentration of ACTH in plasma (171).

In addition to blocking IL-1 production at the transcription and translation levels (172–174), glucocorticoids exert effects on the production of other cytokines (161, 163) such as tumor necrosis factor (175), IL-2 and INF γ (176–178), and IL-3 and GM-CSF (179). Clearly, these observations may explain many of the immunosuppressive effects of glucocorticoids. However, suppression of cytokine production may not be directly responsible for other effects such as the suppression of NK activity (180).

AUTONOMIC NERVOUS SYSTEM-IMMUNE SYSTEM INTERACTIONS

The CNS has two available routes for contacting and regulating structures in the periphery other than skeletal muscle: (*a*) neuroendocrine outflow and (*b*) autonomic outflow. Both routes allow biologically active molecules to interact with cells of the immune system and modulate their responses (109, 181–183). It has long been known that the autonomic nervous system, particularly the postganglionic sympathetic noradrenergic nerves, provide innervation to the vascular and capsular/trabecular smooth muscle in lymphoid organs (184, 185). In the 1970s the existence of adrenergic and other receptors for neurotransmitters on lymphocytes, monocytes/macrophages, and granulocytes was established (186, 187). Only recently, however, was the autonomic innervation of lymphoid organs also shown to be parenchymal, with nerve fibers in direct contact with lymphocytes (185, 188). It now appears that neurotransmitters are available as both paracrine secretions and synaptic mediators for interaction with receptors on cells of the immune system (186, 189, 190). In this section, we briefly discuss the innervation of primary and secondary lymphoid tissue and then describe the extent to which neurally derived substances qualify as neurotransmitters with respect to lymphoid tissues.

Innervation of Lymphoid Organs

Both primary lymphoid organs (thymus, bone marrow) and secondary lymphoid organs (spleen, lymph nodes, gut-associated lymphoid tissue (GALT)) are innervated with noradrenergic (NA) postganglionic sympathetic nerve

fibers (191). Peptidergic nerve fibers also have been found in thymus, spleen, lymph nodes and GALT (191).

These nerve fibers may be: (*a*) primary sensory fibers whose cell bodies are found in a sensory ganglion, such as a dorsal-root ganglion or nodose ganglion, particularly a possibility with substance P (SP) or somatostatin, already known to be primary sensory transmitters in other systems; (*b*) fibers whose neuropeptide is colocalized with norepinephrine (NE) in postganglionic sympathetic nerve fibers, as appears to be the case with most of the neuropeptide Y (NPY) terminals in spleen; (*c*) autonomic postganglionic peptidergic inputs that are independent of the NA innervation; or (*d*) fibers from intrinsic peptidergic neurons within the organ itself, particularly in the case of GALT, known to possess an abundance of peptidergic cell bodies of the enteric nervous system. Intrinsic peptidergic neurons in the other lymphoid organs have not been demonstrated; it is likely that nerve fibers innervating the thymus, spleen, lymph nodes, and bone marrow are derived mainly from ganglion cells of the sympathetic chain or collateral ganglia in the viscera, or from sensory ganglia.

INNERVATION OF PRIMARY LYMPHOID ORGANS Nerve fibers have been found in the substance of the bone marrow, with terminals ending freely among hemopoietic elements (192–196). Using catecholamine histofluorescence, plexuses of NA fibers can be seen to travel with the vasculature into the marrow, and further distribute into the parenchyma (181, 182, 184, 186, 191). It is not clear at present whether peptidergic fibers also distribute into the marrow. Early studies suggested a role for NE in bone marrow function; sympathetic stimulation released cells into the circulation from the marrow (193, 197), similar to secondary lymphoid organs. Beta adrenoceptor stimulation triggered stem cells into cycle or shortened the cell cycle (198), suggesting that key functions such as proliferation, differentiation, and migration may respond to NA neuromodulation.

The thymus receives NA innervation (181, 182, 199–205) from neurons in the superior cervical ganglion and the upper sympathetic chain (203, 206). These fibers enter the thymus with the vasculature, distribute with the capsule and associated septa, and follow the vasculature into the cortex. Fibers are scattered throughout the cortex, with the highest density associated with the vasculature at the cortico-medullary junction. Some NA fibers branch away from the vasculature into the parenchyma, and end among thymocytes. The medulla and associated epithelial zones are innervated sparsely, mainly along the vasculature. The NA innervation of thymus occurs prenatally in mice, earlier than NA innervation to secondary lymphoid organs such as the spleen. Thymocytes, which possess beta adrenoceptors, respond to catecholamines

by inhibiting proliferation and expressing cell surface differentiation antigens (207–211). Enhanced in vitro proliferation responses of thymocytes from 10-day old rats sympathectomized at birth have been reported (182, 186, 212). These sparse data suggest that proliferation, differentiation, and emigration of thymocytes may be under sympathetic NA modulation. The NA innervation of the aging involuted thymus also has been examined (199). As the cortex shrinks, the NA fibers retain their compartmentation and neurotransmitter content, and become densely compact. If NE assists in inhibiting proliferation and enhancing differentiation, then the changing density and concentration of such fibers in the maturing and aging thymus may enhance neurotransmitter availability for these functions.

Bulloch & Moore (203), using horseradish peroxidase retrograde tracing techniques, reported direct innervation of the thymus by neurons in the rostral zone of nucleus ambiguus and by cervical neurons that resembled anterior horn cells. This tracing study, coupled with evidence for acetylcholinesterase-positive (AChE) profiles in the region of the cortico-medullary junction, led to the claim that the thymus is innervated by cholinergic fibers. Since lymphocytes possess muscarinic cholinergic receptors (213–216), such innervation would provide an endogenous ligand for interacting with them. However, although Nance and his colleagues (206) demonstrated abundant innervation to thymus from the superior cervical and upper chain sympathetic ganglia with retrograde tracing techniques, they were unable to find brain stem or vagal innervation. Our efforts to label these putative nerve fibers in thymus anterogradely from the brain stem have not met with success. We find no significant choline acetyltransferase (ChAT) activity in thymus (217). AChE staining is associated mainly with non-neural structures. AChE also is colocalized in NA nerves in the thymus and in other systems, so the mere presence of AChE does not signify cholinergic innervation. These data, then, do not support the existence of cholinergic innervation of the thymus (217).

Several reports have suggested the presence of neuropeptides in the thymus. VIP-like immunoreactive profiles were identified in thymic cortex (181); oxytocin and vasopressin appear to be present in a non-neural compartment of the thymus (218–221). Recent reports suggest the presence of SP and calcitonin gene-related peptide (CGRP), and NPY colocalized with NE, in nerve fibers in the thymus (222, 223). Thymocytes and lymphocytes possess receptors for numerous neuropeptides, linked with classical second-messenger systems, suggesting that neurotransmitters released from these peptidergic nerves may be available to interact with these responsive cells.

INNERVATION OF SECONDARY LYMPHOID ORGANS NA sympathetic fibers arise mainly from ganglion cells in the superior mesenteric/coeliac ganglionic complex, which receives its preganglionic input from cell bodies in the

T6-T12 intermediolateral cell column in the spinal cord in the rat (184, 186, 224). The postganglionic NA fibers travel with the splenic nerve, enter the spleen at the hilar region alongside the splenic vasculature, and distribute into several systems (181, 182, 184, 186, 200, 201, 225–228): (*a*) the capsule; (*b*) the trabecular system of smooth muscle that plays a role in contractile capabilities of spleen; (*c*) the large vessels of the spleen; and (*d*) the splenic white pulp. Most fibers distribute with the trabecular system and the white pulp. In the white pulp, the fibers follow the central arteriolar system, and further branch into the parenchyma in these major sites (187, 227): (*a*) the PALS surrounding the central arteriolar system, where both T-helper and T-suppressor lymphocytes are compacted; (*b*) along the marginal sinus where antigen-presenting macrophages reside, and in the marginal zone, where macrophages and B lymphocytes reside; (*c*) the parafollicular zone, along the outer edge of the B-lymphocyte clusters. NA (tyrosine-hydroxylase positive) nerve terminals form direct synaptic-like contacts with T lymphocytes and macrophages in the PALS (184–186, 188, 191). This is a closer apposition than nerve terminals form with smooth muscle cells in any compartment of the spleen.

SP fibers are found in the spleen, around the central arterioles and large venous sinuses, in the trabeculae, and extending into both the red pulp and the PALS (181, 229). These may be sensory fibers, or may be part of the autonomic innervation; tracing studies are needed to identify their origin. CGRP-containing fibers are found in these same compartments, and may contain colocalized SP (229). We also found NPY-containing nerve fibers in the spleen, following the compartmental distribution seen for NA nerves (191, 230, 231). Our impression is that most of the NPY immunoreactivity is colocalized with TH in (NA) nerves, although this also remains to be demonstrated experimentally. Additional putative neurotransmitters found in the spleen include somatostatin, CCK, neurotensin, met-enk, VIP and others (181, 232, 233). IL-1 immunoreactivity also has been identified in nerve-like profiles in the spleen (234), perhaps colocalized in the NA fibers. In view of the extensive array of receptors for these and other neurotransmitters found on lymphocytes, monocytes/macrophages, granulocytes, and other cell types, the possibilities for neurally derived peptides interacting with specific receptors on cells of the immune system raise the spectre of a complexity of interactions rivaled by neurotransmission in the CNS or by cytokine interactions in the immune system.

NA fibers arise from ganglion cells in either the sympathetic chain or in collateral sympathetic ganglia, and distribute into the lymph node with the hilar vasculature (181, 182, 184, 186, 191, 235, 236). The fibers distribute through the medullary cords, alongside the medullary sinuses, extend past the cortico-medullary junctions into the paracortical zone, and arborize among T

lymphocytes. A subcapsular plexus of NA fibers sends branches into the cortical zone. Few, if any, distribute into the follicles. Thus, several compartments of lymph nodes are innervated, including the medullary cords, the paracortex and subcapsular cortex, the subcapsular sinus, and the capsule. A comparison with the splenic innervation shows numerous functional similarities; (*a*) site of lymphocyte entry (spleen-marginal zone; lymph node—corticomedullary junction); (*b*) site of antigen capture (spleen—marginal zone, sinus; lymph node—subcapsular sinus); (*c*) site of antigen presentation and lymphocyte activation, T cells (spleen—PALS; lymph node—paracortex); (*d*) site of antigen presentation and lymphocyte activation, B cells (spleen—parafollicular/marginal zone; lymph node—medullary cords); (*e*) Site of lymphocyte egress (spleen—outer marginal zone; lymph node—medullary sinus) (186, 187, 226).

The main structures studied as representative of GALT have been the rabbit appendix and Peyer's patches in several species. The basic patterns of innervation by NA fibers are similar (181, 182, 184, 186, 191, 237, 238). These fibers arise from mesenteric ganglia, and distribute in plexuses of fibers that either travel with the smooth muscle and turn radially, or move directly radially towards the mucosal surface. These fibers travel between the follicles, in an internodular plexus, without sending arborizations into the B-lymphocyte zones, then directly traverse the T-dependent (T-lymphocyte) zone, and enter the lamina propria, where they branch freely among the cellular constituents, including some lymphocytes, plasma, mast, enterochromaffin, and other cells. The NA fibers extend out to the subepithelial region of plasma cells, but not to the lumen.

Extensive evidence exists for the presence of neuropeptides in the enteric nervous system (239). Whether these peptides contribute to modulation of immune function has been ascertained only for a few. As an example, Ottaway and colleagues (240) have described a plexus of VIP fibers near the postcapillary venules, the site of entry of lymphocytes with VIP receptors (241, 242) that influence the homing behavior of those lymphocytes (243, 244). These fibers probably play a role in the ingress and retention of lymphocytes in GALT. Stead and colleagues (245) found a close association between SP and CGRP nerve fibers and mast cells in the gut, suggesting an interaction that may result in both neurotransmitters and compounds from mast cells being secreted into the local microenvironment and mutually influencing each other.

Criteria for Neurotransmission

In order for a neurally derived substance to qualify as a neurotransmitter, it must satisfy four criteria. As detailed below, most if not all of these criteria have been met for NE, with cells of the immune system serving as bona fide

targets (186, 187). Although some other neuropeptides also fulfill most of these criteria, the evidence for acetylcholine as a neurotransmitter is weak or negative.

Criterion 1. Presence of chemically specific nerve fibers and their compartmentation The observations that NA sympathetic fibers innervate primary and secondary lymphoid tissues, ending mainly in compartments where T lymphocytes and antigen-presenting macrophages are present, and also ending among plasma cells in GALT and around B lymphocytes during development, clearly satisfy this first criterion. In addition, there is a suggestion of peptidergic (VIP, NPY, SP, CGRP) nerve fibers in thymus, peptidergic (SP, NPY, CGRP, VIP, and others) nerve fibers in the spleen, and peptidergic, cholinergic, and serotonergic fibers in some areas of gut. Peptidergic nerve fibers have not been examined carefully in lymph nodes and bone marrow.

Criterion 2. Release of neurotransmitter and availability for interaction The strongest evidence for release of neurotransmitter in a lymphoid organs is for the splenic release of NE. NE derives almost exclusively from the neural compartment of the spleen, since it is depleted by greater than 95% by denervation with ganglionectomy or chemical sympathectomy (186, 201, 224). Stimulation studies and in vivo dialysis indicate that NE is released into the extracellular fluid of the spleen (184, 246), suggesting the paracrine availability of NE as a neurotransmitter, in addition to the possible availability from direct synaptic-like interactions with lymphocytes in the PALS. In order to understand the local availability of neurotransmitters in the microenvironment of specific lymphoid cells, the proximity of those cells to nerve terminals, and the local paracrine concentration of neurotransmitter must be known. Denervation studies and chemical assays of NE and some neuropeptides in other lymphoid organs suggest that these signal molecules are present, and probably are available for interaction with lymphoid cells; strict criteria for release, however, still must be met.

Criterion 3. Receptors on target cells The presence of beta adrenoceptors, particularly the beta-2 subclass, on lymphocytes was known (209, 247–258) even before direct innervation of lymphocytes was suspected. B lymphocytes possess more beta adrenoceptors than T lymphocytes; T-suppressor and helper cells possess approximately the same number. Monocytes/macrophages and granulocytes also possess adrenoceptors. Evidence for alpha adrenoceptors on lymphocytes has been indirect, depending mainly upon use of alpha blockers or agonists in the evaluation of lymphocyte functions (182, 186, 259). Beta adrenoceptors on lymphocytes are reportedly linked through a

cyclic AMP second-messenger system, providing strong evidence for an immunomodulatory role for NE. Studies that have evaluated beta adrenoceptors on splenic lymphocytes found receptor upregulation following denervation (253, 256), as is the case with beta adrenoceptors on other target cells in the periphery (260). Thus, this criterion for neurotransmission is established solidly for beta adrenoceptors, is presumptive for alpha adrenergic receptors, and provides a signal transduction pathway for NE that is stimulated by a host of other bioactive molecules known to be involved in immunoregulation (e.g. 261). This point does raise a caution; in studies of lymphocytes from the peripheral blood, neurotransmitter responses might be different from responses in splenic or lymph-node derived lymphocytes. Similarly, lymphocytes in culture may demonstrate marked alterations in receptors responses, because they are removed from their normal microenvironment and probably can respond to the state of denervation through upregulation. Because some neurotransmitters can augment or synergize cytokine effects on target cells, in vitro studies that remove normally present neurotransmitters such as NE must be interpreted cautiously.

Lymphocytes possess receptors for VIP, somatostatin, SP, and many other peptides (241, 242, 262–266). However, some cautions are in order for other peptides. A binding site is not the equivalent of a real receptor unless saturability, displacability, and stereospecificity can be demonstrated, and intracellular effects through appropriate second-messenger links can be identified. Similarly, the demonstration of a change in lymphocyte function following the application of a neuropeptide (often in pharmacologic doses) does not mean that the neuropeptide acted through a classical receptor. For example, agonists or agents that alter serotonin synthesis can produce alteractions in leukocyte functions despite the lack of evidence for classical serotonin receptors. The serotonin acts through high-affinity uptake sites, and exerts its effects intracellularly (267). This is particularly a caution in the very complex interactions of the opioid peptides with lymphocytes. The demonstration of an effect of pharmacological doses of a peptide without evidence for endogenous presence of availability, release, and receptors on target cells does not constitute evidence for neurotransmission. Some of the opioid peptides could have a nontraditional mode of action, or a hormonal effect in addition to, or instead of, a traditional neurotransmitter role. Evidence for opioid receptors on lymphocytes has been sparse and inconsistent. Interactions between hormones and receptors for neurotransmitters also must be taken into account (268). Glucocorticoids can enhance the expression of beta receptors on some cells, and may regulate neurotransmitter interactions on lymphocytes indirectly (269–273).

Receptors on lymphocytes for dopamine, acetylcholine (muscarinic), clonidine, and benzodiazepine have been reported. The presence of these receptors

in an environment where contact with the appropriate ligand may not be available for receptor activation raises an interesting but unanswered question about why they are expressed. Perhaps they function only when that cell is in a specific compartment such as GALT, since lymphocytes can move through a variety of organs. Perhaps they are activated only at a specific time during development. Or perhaps they are only an epiphenomenon of genetic expression that accompanies the presence of other functional peptides or proteins.

Criterion 4. A functional role for the putative neurotransmitter Although a comprehensive review (186, 187) of the numerous examples of an immunomodulatory role NE is beyond the scope of this chapter, a few studies should be highlighted. NE interacts with beta adrenoceptors on thymocytes through a cAMP second messenger to inhibit mitogenesis and to enhance expression of cell surface differentiation antigens (181, 182, 186, 207, 208, 274–277). Physiological concentrations of NE have been reported to enhance the primary in vitro IgM anti-SRBC response; beta blockers, but not alpha blockers, prevented this enhancement (259, 278–281). The alloreactive cytotoxic T lymphocyte (CTLs) response to allogeneic cells could be enhanced by mixed agonists and beta agonists (282) and suppressed by chemical sympathectomy (182, 212, 283). NE has been reported to inhibit the synthesis of complement components through an alpha mechanism (284), and to inhibit activation of macrophages in a tumor-cell lysis model (144). Chemical sympathectomy (181, 182, 186, 212, 235, 274, 283) has been associated with a suppressed in vivo DTH response, with an enhanced in vivo proliferation of lymphocytes in some but not all lymph nodes, and with enhanced NK cell activity (both in vivo and in vitro). In addition to its apparent direct effects on leukocytes, the egress of activated lymphocytes from secondary lymphoid organs appears to be under NA control (285–287).

The neuropeptides VIP, somatostatin, and SP, known mainly for their presence and actions in the nervous system, have recently been shown to be modulators of immune function (266, 288–290). SP is found mainly in primary afferent neurons that supply the skin, the mucous membranes, regions of the GI tract, and nerve fibers supplying the thymus and spleen, and has a well-known role in modulation of nociception through C fibers. SP has several actions on target cells that directly and indirectly stimulate inflammation (289, 291–295). SP enhances vascular permeability and increases local vasodilation. Both effects enhance the ability of lymphocytes to migrate to the area. SP receptors have been found on T helper, T suppressor, and B lymphocytes (296–298) and macrophages (291). SP is a T-cell mitogen, and can enhance T-cell proliferation to lectins (264, 265, 299). It also enhances Con A-induced IgA production by lymphocytes from mesenteric lymph nodes, spleen, and Peyer's patches (299, 300). In addition, SP enhances

macrophage phagocytosis and polymorphonuclear (PMN) leukocyte chemotaxis (292, 293). Based on observations that stress may exacerbate rheumatoid arthritis, and that SP released by peripheral nerves may produce many tissue changes of acute inflammation such as stimulation of phagocytosis by PMNs, it has been proposed that SP contributes to the pathophysiology of this disorder (288, 289, 301).

Somatostatin, also found in C fibers and small myelinated A-delta fibers, acts through receptors for somatostatin on lymphocytes, and appears to be inhibitory to many of the actions of SP (288, 290, 299, 302, 303). Somatostatin inhibits the release of SP from the peripheral terminals of primary afferent neurons. It also has a direct receptor-mediated effect on lymphocytes and monocytes via receptors. Somatostatin exerts an inhibitory effect on PHA-induced human T-cell mitogenesis, suppresses endotoxin-induced leukocytosis, and suppresses the release of colony-stimulating factor activity by splenic lymphocytes.

In general, VIP also inhibits a variety of immune functions (242, 262, 263, 304). VIP is found in peripheral nerves (181, 233, 240, 305) associated with the thymus, the spleen, lymph nodes and mucosal tissues, such as the GI tract. T lymphocytes possess high-affinity receptors for VIP (231, 242). VIP decreases the T-cell proliferative responses to mitogens, but has no affect on B-cell mitogen responses (242, 262, 304). VIP activation is related to cAMP stimulation (263), generally inhibitory to proliferative responses of lymphocytes. VIP receptors can be down-regulated (by internalization) following incubation of T lymphocytes with VIP (243, 244). The localization of these T lymphocytes with down-regulated VIP receptors was decreased greatly in the mesenteric lymph nodes and Peyer's patches, while localization to spleen, intestine, liver, and lungs was unaltered. This alteration in VIP-receptor expression affects the interaction of lymphocytes with the specialized high endothelium on the postcapillary venules where lymphocytes enter lymph nodes and Peyer's patches. Thus, lymphocyte traffic into GALT depends upon the intactness of high-affinity receptors for VIP.

Potential Interactions of Neurotransmitters with Cells of the Immune Systems

The microenvironment of cells of the immune system The presence of nerve fibers in the parenchyma of lymphoid organs, and the availability of neurotransmitters for interactions with cells of the immune system add a new dimension to our understanding of the microenvironment of immune cells. The splenic microenvironment contains paracrine, endocrine, and autocrine secretions, and also products of nerve fibers. The paracrine environment includes cytokines as well as the secretions of accessory or supporting cells

(e.g. serotonin, histamine, prostaglandins) and most probably, lymphocyte-derived neuropeptides (93, 139, 306–310). The endocrine environment includes hormones derived from the pituitary (ACTH, endorphins, GH, PRL, LH and FSH, TSH) (109), its target organs (glucocorticoids, gonadal steroids, thyroid hormones, and others), or the immune system itself (thymosin peptides) (311, 312). These are blood-borne signals that do not depend upon cell-cell interactions for their effects. Neurotransmitters represent additional forms of signal molecules directed towards cells of the immune system. It is clear that neurotransmitters such as NE and several of the neuropeptides are present in physiologically adequate concentrations as paracrine-like secretions for interactions with nearby cells. The presence of direct nerve terminal contacts with lymphocytes and macrophages adds a new form of synaptic-like communication that may be more directed and discrete than paracrine communication, and may be superimposed upon the paracrine presence of neurotransmitters. As a further form of communication, the cells of the immune system may secrete compounds that influence their own functions (autocrine), or influence neurotransmitter secretion from adjacent nerve terminals.

These forms of communication do not occur alone, but interact with each other. Hormones may alter the expression of neurotransmitter receptors as discussed above. Neurotransmitters may alter the responsiveness of hormones and cytokines interacting with lymphocytes or macrophages (313, 314). Cytokines may interact with nerve terminals to alter neurotransmitter release, in addition to their effects on cells of the immune system (315–317). It is clear that there are both long and short feedback loops between the nervous system and the immune system (e.g. 318–321). The long loops may be represented by the CRF-ACTH-glucocorticoid-lymphoid cell-cytokine-CNS (limbic-hypothalamic) communication channel. Interleukin-1 has been proposed as a likely cytokine in this loop, based on its central effects on CRF neurons and on monoamine metabolism related to the CRF-ACTH-glucocorticoid axis (95, 170). The short loops may be represented by a direct exchange, such as a nerve terminal secreting a neurotransmitter within 6 nm of a lymphocyte, and the lymphocyte secreting a cytokine that interacts with the terminal to alter neurotransmitter metabolism (185, 188).

In addition to the principle neurotransmitter identified in a fiber or terminal, other colocalized neurotransmitters are often present. Those neurotransmitters may be synthesized in that same nerve terminal (e.g. NE and NPY, SP and CGRP), may be taken up by a high-affinity uptake site (e.g. epinephrine from hormonal sources taken into NA nerve terminals for subsequent release as a neurotransmitter) (322), or may be taken up by a low-affinity uptake site (e.g. serotonin uptake from a platelet source for subsequent release as a neurotransmitter) (323). The extent of release of the colocalized peptides may

depend upon differential regulation of release following appropriate physiological stimuli, and upon the availability of the other humoral agents such as epinephrine and serotonin during a particular period of time. Thus, the behavioral and environmental conditions surrounding the organism may have a marked effect on the content of secretion from a nerve terminal.

Potential mechanisms of interaction between neurotransmitters and target cells of the immune system With the emphasis on the identification of receptors and neurotransmitters available for potential interaction in lymphoid organs, the most straightforward form of communication proposed between nerves and lymphoid cells is a classical ligand-receptor interaction with subsequent intracellular alterations that influence the function of the target cell. The number and complexity of direct ligand-receptor interactions for a single neurotransmitter, such as NE, on the many subsets of lymphoid cells, is considerable (181, 186, 187, 190). Neurotransmitters also may act indirectly, through the release of other signal molecules from mast, enterochromaffin, or other cells that are intermediaries between a nerve terminal and a lymphocyte or macrophage (245, 324, 325). These links could be very complex. Neurotransmitters may alter blood flow, vascular permeability, or lymphocyte traffic across specialized regions of the vasculature. Neurotransmitters may modulate the activity, expression, or action of other neurotransmitters, hormones, cytokines or their receptors, thereby acting as true neuromodulators (neural substances that have minimal effect by themselves, but potentiate the effect of other neurally active molecules). Finally, neurotransmitters may interact directly with each other to modify or occupy active sites of these molecules (326). All these processes may occur singly or in combination, depending upon the complexity of the local microenvironnent.

If we assume the most direct mechanism of communication for neurotransmitters, the direct ligand-receptor interaction, then we must ask what the target cell is capable of doing in response to that direct interaction. In the case of lymphocytes, the potential responses of the target cell are many: (*a*) proliferation; (*b*) differentiation; (*c*) activation or inactivation; (*d*) altered expression of a variety of receptors (e.g. antigen-specific receptors on T and B cells, cytokine receptors, receptors for other neurotransmitters); (*e*) secretion of specific molecules, such as antibodies (B lymphocytes), lymphokines (T lymphocytes), monokines (macrophages), or hormones (endocrine cells): (*f*) movement, migration, or altered cell trafficking; and (*g*) upregulation of products of the major histocompatibility complex. These are only some of the possible responses that may occur, singly or in combination, in numerous compartments of many lymphoid organs in response to a single neurotransmitter. When we look at the many neurotransmitters that are present in the thymic-, splenic- or lymph-node microenvironment, the possi-

ble extent and complexity of modulation is considerable. Sorting out these complicated interactions promises to be every bit as challenging a task as exploring the role of neurotransmitters in the brain, or cytokines in the immune system.

SUMMARY

The observations and research described in this communication derive from a nontraditional view of the immune system. It has become abundantly clear that there are probably no organ systems or homeostatic defense mechanisms that are not, in vivo, subject to the influence of interactions between behavioral and physiological events. The complex mechanisms underlying these interactions and their relationship to health and illness, however, are imperfectly understood. The most imperfectly understood, perhaps, are the interrelationships among brain, behavior, and immune processes. Without attempting to cover all the literature, we have used stress effects and conditioning phenomena as illustrations to point out that behavior can influence immune function. We have also described data indicating that the immune system can receive and respond to neural and endocrine signals. Conversely, behavioral, neural, and endocrine responses seem to be influenced by an activated immune system. Thus, a traditional view of immune function that is confined to cellular interactions occurring within lymphoid tissues is insufficient to account for changes in immunity observed in subhuman animals and man under real world conditions.

These data question seriously the notion of an autonomous immune system. Most of the research on the regulation of immune responses has been predicated on the assumption that such regulation is accomplished by the interacting components of the immune system itself, e.g. interactions among helper and suppressor T-lymphocytes, B-cells, and accessory cells that can result in the production of antibody and effector T cells. The immune system is, indeed, capable of considerable self-regulation, and immune responses can be made to take place in vitro. The functions of that component of adaptive processes known as the immune system that are of ultimate concern, however, are those that take place in vivo. There are now compelling reasons to believe that in vivo immunoregularity processes influence and are influenced by the neuroendocrine environment in which such processes actually take place—an environment that, on the one hand, can generate signals that resting and/or activated leukocytes can receive, and, on the other hand, is exquisitely sensitive to the individual's perception of and capacity to adapt to the demands of the environment. The immune system appears to be modulated, not only by feedback mechanisms mediated through neural and endocrine processes, but by feedforward mechanisms as well. The immunologic effects of

learning, an essential feedforward mechanism, suggest that, like direct neural and endocrine processes, behavior can, under appropriate circumstances, serve an immunoregulatory function in vivo. Conceptually, the capacity to suppress or enhance immune responses by conditioning has raised innumerable questions about the normal operation and modifiability of the immune system via neural and endocrine processes.

We do not yet know the nature of all the channels of communication between the brain and the immune system or the functional significance of the neural and endocrine interrelationships that have been established. A detailed review of relevant central and neuroendocrine circuitry is beyond the scope of this review, but a brief summary can be provided as a guide to further reading and research. Autonomic preganglionic neurons receive direct fiber projections from brain stem nuclei (nucleus solitarius, raphe nuclei, tegmental noradrenergic nuclei), hypothalamic nuclei (paraventrivular nucleus oxytocin and vasopressin neurons, lateral hypothalamus, posterior hypothalamus, dorsal hypothalamus), limbic forebrain structures (central amygdaloid nucleus), and regions of the cerebral cortex (frontal, cingulate, and insular cortical areas, mainly zones of "limbic" cortex). In addition, indirect regulation of these systems arises from regions such as the parabrachial nuclei, central gray, and reticular formation of the brain stem, numerous hypothalamic nuclei and cell groups, limbic forebrain areas such as the hippocampal formation and septum, and cortical association areas. These structures interconnect with the hypothalamus, the structure that lies at the crossroads of the limbic forebrain and brain stem nuclei.

This integrated circuitry has extensive ascending and descending connections among the regions cited. These regions also share many similarities. They are sites intimately involved in visceral, autonomic, and neuroendocrine regulation. The cortical and limbic forebrain regions mediate both affective and cognitive processes and may be involved in the response to stressors, in affective states and disorders such as depression, in aversive conditioning, and in the emotional context of sensory inputs from the outside as well as the inside world. From an immunologic perspective, these regions are the sites in which lesions result in altered responses of cells of the immune system; they are the regions that respond to immunization or cytokines by altered neuronal activity or altered monoamine metabolism; and they are the regions that possess the highest concentration of glucocorticoid receptors and link some endocrine systems with neuronal outflow to the autonomic and neuroendocrine systems. Thus, this circuitry is the major system of the CNS suspected to play a key role in responding to immune signals and regulating CNS outflow to the immune system.

Without being able to specify the precise mechanisms, we have described converging research from different levels of biological organization, all of

which support a nontraditional, integrated approach to an elaboration of the adaptive functions of the immune system. The data summarized provide compelling evidence that the immune system, like any other system operating in the interests of homeostasis, is integrated with other psychophysiological processes and is therefore influenced by and capable of influencing the brain.

Literature Cited

1. Ader, R., Cohen, N., Felten, D. L. 1987. Brain, behavior, and immunity. *Brain Behav. Immun.* 1:1–6
2. Weiner, H. 1977. *Psychobiology and Human Disease*. New York: Elsevier
3. Plaut, S. M., Friedman, S. B. 1981. Psychosocial factors in infections disease. See Ref. 60, pp. 3–30
4. Sklar, L. S., Anisman, H. 1981. Stress and cancer. *Psychol. Bull.* 89:369–406
5. Justice, A. 1981. Review of the effects of stress on cancer in laboratory animals: Importance of time of stress application and type of tumor. *Psychol. Bull.* 98:108–38
6. Mor, V., McHorney, C., Sherwood, S. 1986. Secondary morbidity among the recently bereaved. *Am. J. Psychiatry* 143:158–63
7. Jacobs, S., Ostfeld, A. 1977. An epidemiological review of the mortality of bereavement. *Psychosom. Med.* 39:344–57
8. Helsing, K. J., Szklo, M., Comstock, G. W. 1981. Factors associated with mortality after widowhood. *Am. J. Public Health* 71:802–9
9. Bartrop, R. W., Luckhurst, E., Lazarus, L., Kiloh, L. G., Penny, R. 1977. Depressed lymphocyte function after bereavement. *Lancet* 1:834–36
10. Schleifer, S. J., Keller, S. E., Camerino, M., Thornton, J. C., Stein, M. 1983. Suppression of lymphocyte stimulation following bereavement. *J. Am. Med. Assoc.* 250:374–77
11. Irwin, M., Daniels, M., Smith, T. L., Bloom, E., Weiner, H. 1987. Impaired natural killer cell activity during bereavement. *Brain Behav. Immun.* 1:98–104
12. Kiecolt-Glaser, J. K., Glaser, R. 1986. Psychological influences on immunity. *Psychosomatics* 27:621–24
13. Schleifer, S. J., Keller, S. E., Meyerson, A. T., Raskin, M. J., Davis, K. L., Stein, M. 1984. Lymphocyte function in major depressive disorder. *Arch. Gen. Psychiatry* 41:484–86
14. Schleifer, S. J., Keller, S. E., Siris, S. G., Davis, K. L., Stein, M. 1985. Depression and immunity: Lymphocyte function in ambulatory depressed patients, hospitalized schizophrenic patients, and patients hospitalized for herniorrhaphy. *Arch. Gen. Psychiatry* 42:129–33
15. Jankovic, B. D., Jakulic, S., Horvat, J. 1982. Delayed skin hypersensitivity reactions to brain S-100 protein in psychiatric patients. *Biol. Psychiatry* 17: 687–97
16. Kiecolt-Glaser, J. K., Stephens, R. E., Lipetz, P. D., Speicher, C. E., Glaser, R. 1985. Distress and DNA repair in human lymphocytes. *J. Behav. Med.* 8:311–20
17. Kronfol, Z., Silva, J. Jr., Greden, J., Dembrinski, S., Gardner, R., Carroll, B. 1983. Impaired lymphocyte function in depressive illness. *Life Sci.* 33:241–47
18. Syvalhati, E., Eskola, J., Ruuskanen, O., Laine, T. 1985. Nonsuppression of cortisol in depression and immune function. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 9:413–22
19. Sengar, D. P. S., Waters, B. G. H., Dunne, J. V., Bouer, I. M. 1982. Lymphocyte subpopulations and mitogenic responses of lymphocytes in manic-depressive disorders. *Biol. Psychiatry* 17:1017–22
20. Albrecht, J., Helderman, J. H., Schlesser, M. A., Rush, A. J. 1985. A controlled study of cellular immune function in affective disorders before and during somatic therapy. *Psychiatry Res.* 15: 185–93
21. Roos, R. P., Davis, K., Meltzer, H. Y. 1985. Immunoglobulin studies in patients with psychiatric disease. *Arch. Gen. Psychiatry* 42:124–28
22. Friedman, H. 1990. Immunosuppression by marijuana and components. In *Psychoneuroimmunology II*, ed. R. Ader, N. Cohen, D. L. Felten, New York: Academic. In press
23. Baranic, M., Pericic, D., Poljak-Blazi, M. 1979. The immunological reactivity of mice stressed by overcrowding and

treated with halperidol. *Period. Biol.* 81:213–14
24. Farris, E. J. 1938. Increase in lymphocytes in healthy persons under certain emotional states. *Am. J. Anat.* 63:297–323
25. Glaser, R., Thorn, B. E., Tarr, K. L., Kiecolt-Glaser, J. K., D'Ambrosio, S. M. 1985. Effects of stress on methyltransferase synthesis: An important DNA repair enzyme. *Health Psychol.* 4:403–12
26. Glaser, R., Rice, J., Sheridan, J., Fertel, R., Stout, J., et al. 1987. Stress-related immune suppression: Health implications. *Brain Behav. Immun.* 1:7–20
27. Michaut, R.-J., Dechambre, R.-P., Doumerc, S., Lesourd, B., Devillechabrolle, A., Moulias, R. 1981. Influences of early maternal deprivation on adult humoral immune response in mice. *Physiol. Behav.* 26:189–91
28. Ackerman, S. H., Keller, S. E., Schleifer, S. J., Shindledecker, R. D., Camerino, M., et al. 1988. Premature maternal separation and lymphocyte function. *Brain Behav. Immun.* 2:161–65
29. Pierpaoli, W., Fabris, N., Sorkin, E. 1970. Developmental hormones and immunological maturation. *Ciba Found. Study Group* 36:126–43
30. Reite, M., Harbeck, R., Hoffman, A. 1981. Altered cellular immune response following peer separation. *Life Sci.* 29: 1133–36
31. Laudenslager, M. L., Reite, M., Harbeck, R. J. 1982. Suppressed immune response in infant monkeys associated with maternal separation. *Behav. Neural Biol.* 36:40–48
32. Coe, C. L., Weiner, S. G., Rosenberg, L. T., Levine, S. 1985. Endocrine and immune responses to separation and maternal loss in nonhuman primates. In *The Psychobiology of Attachment and Separation*, ed. M. Reite, T. Field, pp. 163–220. New York: Academic
33. Coe, C. L., Rosenberg, L. T., Levine, S. 1988. Prolonged effect of psychological disturbance on macrophage chemiluminescence in the squirrel monkey. *Brain Behav. Immun.* 2:151–60
34. Monjan, A. A., Collector, M. I. 1977. Stress-induced modulation of the immune response. *Science* 196:307–8
35. Keller, S. E., Weiss, J. M., Schleiffer, S. J., Miller, N. E., Stein, M. 1981. Suppression of immunity by stress: Effect of a graded series of stressors on lymphocyte stimulation in the rat. *Science* 213:1397–1400
36. Shavit, Y., Lewis, J. W., Terman, G. W., Gale, R. P., Liebeskind, J. C. 1984. Opioid peptides mediate the suppressive effect of stress on natural killer cell cytotoxicity. *Science* 223: 188–90
37. Lysle, D. T., Lyte, M., Fowler, H., Rabin, B. S. 1987. Shock-induced modulation of lymphocyte reactivity: Suppression, habituation, and recovery. *Life Sci.* 41:1805–14
38. Moynihan, J. A., Schactman, T. R., Cohen, N., Ader, R. 1989. Effects of footshock stress on the development of immunological memory following low dose antigen priming in mice. *Brain Behav. Immun.* 4: In press
39. Okimura, T., Nigo, Y. 1986. Stress and immune responses. I. Suppression of T cell function in restraint-stressed mice. *Jpn. J. Pharmacol.* 40:505–11
40. Esterling, B., Rabin, B. S. 1987. Stress-induced alteration of T-lymphocyte subsets and humoral immunity in mice. *Behav. Neurosci.* 101:115–19
41. Salcman, S., Minkiewicz-Janda, A., Richter, M., Anisman, H. 1988. Critical periods associated with stressor effects on antibody titers and on the plaque-forming cell response to sheep blood cells. *Brain Behav. Immun.* 2:254–66
42. Keller, S. E., Weiss, J. M., Schleiffer, S. J., Miller, N. E., Stein, M. 1983. Stress-induced suppression of immunity in adrenalectomized rats. *Science* 221: 1301–4
43. Cunnick, J. E., Lysle, D. T., Armfield, A., Rabin, B. S. 1988. Shock-induced modulation of lymphocyte responsiveness and natural killer activity: Differential mechanisms of induction. *Brain Behav. Immun.* 2:102–13
44. Mormede, P., Dantzer, R., Michaud, B., Kelley, K. W., Le Moal, M. 1988. Influence of stressor predictability and behavioral control on lymphocyte reactivity, antibody responses and neuroendocrine activation in rats. *Physiol. Behav.* 43:577–83
45. Blecha, F., Barry, R. A., Kelley, K. W. 1982. Stress-induced alterations in delayed-type hypersensitivity to SRBC and contact sensitivity to DNFB in mice. *Proc. Soc. Exp. Biol. Med.* 169:239–46
46. Shavit, Y., Ryan, S. M., Lewis, J. W., Laudenslager, M. L., Terman, G. W., et al. 1983. Inescapable but not escapable stress alters immune function. *Physiologist* 26:A64
47. Laudenslager, M. L., Ryan, S. M., Drugan, R. C., Hyson, R. L., Maier, S. F. 1983. Coping and immunosuppression—Inescapable but not escapable

shock suppresses lymphocyte proliferation. *Science* 221:568–70
48. Maier, S. F., Laudenslager, M. L. 1988. Inescapable shock, shock controllability, and mitogen stimulated lymphocyte proliferation. *Brain Behav. Immun.* 2:87–91
49. Feldman, R. D., Limbird, L. E., Nadeau, J., FitzGerald, G. A., Robertson, D., Wood, A. J. J. 1983. Dynamic regulation of leukocyte beta adrenergic receptor-agonist interactions by physiological changes in circulating catecholamines. *J. Clin. Invest.* 72:164–70
50. Blecha, F., Kelley, K. W., Satterlee, D. G. 1982. Adrenal involvement in the expression of delayed-type hypersensitivity to SRBC and contact sensitivity to DNFB in stressed mice. *Proc. Soc. Exp. Biol. Med.* 169:247–52
51. Greenberg, A. H., Dyck, D. G., Sandler, L. S., Pohajdak, B., Dresel, K. M., Grant, D. 1984. Neurohormonal modulation of natural resistance to a murine lymphoma. *J. Natl. Cancer Inst.* 72: 653–59
52. Landi, M. S., Kreider, J. W., Lang, C. M., Bullock, L. P. 1982. Effects of shipping on the immune function in mice. *Am. J. Vet. Res.* 43:1654–57
53. Rocha, B. 1985. The effects of stress in normal and adrenalectomized mice. *Eur. J. Immunol.* 15:1131–35
54. Ito, Y., Mino, K., Ago, Y., Nakagawa, T., Fujiwara, M., Ueki, S. 1983. Attack stress and IgE antibody production in rats. *Pharmacol. Biochem. Behav.* 19: 883–86
55. Rabin, B. S., Salvin, S. B. 1987. Effect of differential housing and time on immune reactivity to sheep erythrocytes and Candida. *Brain Behav. Immun.* 1:267–75
56. Odio, M., Brodish, A., Ricardo, M. J. 1987. Effects on immune responses by chronic stress are modulated by aging. *Brain Behav. Immun.* 1:204–15
57. Keller, S. E., Schleifer, S. J., Liotta, A. S., Bond, R. N., Farhoody, N., Stein, M. 1988. Stress-induced alterations of immunity in hypophysectomized rats. *Proc. Natl. Acad. Sci. USA* 85:9297–301
58. Metal'nikov, S., Chorine, V. 1926. Rôle des réflexes conditionnels dans l'immunité. *Ann. Inst. Pasteur Paris* 40:893–900
59. Metal'nikov, S., Chorine, V. 1928. Rôle des réflexes conditionnels dans la formation des anticorps. *C. R. Soc. Biol.* 99:142–45
60. Ader, R. 1981. A historical account of conditioned immunobiologic responses. In *Psychoneuroimmunology*, ed. R. Ader, pp. 3231–54. New York: Academic
61. Ader, R., Cohen, N. 1975. Behaviorally conditioned immunosuppression. *Psychosom. Med.* 37:333–40
62. Ader, R., Cohen, N. 1985. CNS-immune system interactions: Conditioning phenomena. *Behav. Brain Sci.* 8: 379–95
63. Ader, R., Cohen, N. 1990. The influence of conditioning on immune responses. See Ref. 22
64. Dyck, D. G., Greenberg, A. H., Osachuk, T. A. G. 1986. Tolerance to drug-induced (Poly I:C) natural killer cell activation: Congruence with a Pavlovian conditioning model. *J. Exp. Psychol. Anim. Behav. Proc.* 12:25–31
65. Dyck, D. G., Dreidger, S. M., Nemeth, R., Osachuk, T. A. G., Greenberg, A. H. 1987. Conditioned tolerance to drug-induced (Poly I:C) natural killer cell activation: Effect of drug dosage and context specificity parameters. *Brain Behav. Immun.* 1:251–66
66. Ader, R., Cohen, N. 1982. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science* 215:1534–36
67. Ader, R. 1985. Conditioned immunopharmacological effects in animals: Implications for a conditioning model of pharmacotherapy. In *Placebo: Theory, Research, and Mechanisms*, ed. L. White, B. Tursky, G. E. Schwartz, pp. 306–23. New York: Guilford
68. Gorczynski, R. M., Kennedy, M., Ciampi, A. 1985. Cimetidine reverses tumor growth enhancement of plasmacytoma tumors in mice demonstrating conditioned immunosuppression. *J. Immunol.* 134:4261–64
69. MacQueen, G. M., Marshall, J., Perdue, M., Siegel, S., Bienenstock, J. 1989. Pavlovian conditioning of rat mucosal mast cells to secrete rat mast cell protease II. *Science* 243:83–85
70. Lysle, D. T., Cunnick, J. E., Fowler, H., Rabin, B. S. 1988. Pavlovian conditioning of shock-induced suppression of lymphocyte reactivity: Acquisition, extinction, and preexposure effects. *Life Sci.* 42:2185–94
71. Gorczynski, R. M., Macrae, S., Kennedy, M. 1982. Conditioned immune response associated with allogeneic skin grafts in mice. *J. Immunol.* 129:704–9
72. Krank, M. D., MacQueen, G. M. 1988. Conditioned compensatory responses elicited by environmental signals for

cyclophosphamide-induced suppression of antibody production in mice. *Psychobiology* 16:229–35
73. MacQueen, G. M., Siegel, S. 1989. Conditional immunomodulation following training with cyclophosphamide. *Behav. Neurosci.* 103:638–47
74. Gorczynski, R. M., Macrae, S., Kennedy, M. 1984. Factors involved in the classical conditioning of antibody responses in mice. In *Breakdown in Human Adaptation to Stress: Towards a Multidisciplinary Approach*, ed. R. Ballieux, R. Fielding, A. L'Abbate, pp. 704–12 Boston: Martinus Nijhof
75. Ader, R., Cohen, N., Grota, L. J. 1979. Adrenal involvement in conditioned immunosuppression. *Int. J. Pharm.* 1:141–45
76. Ader, R., Cohen, N., Bovbjerg, D. 1979. Conditioned suppression of humoral immunity in the rat. *J. Comp. Physiol. Psychol.* 96:517–21
77. Kusnecov, A. W., Sivyer, M., King, M. G., Husband, A. J., Cripps, A. W., Clancy, R. L., 1983. Behaviorally conditioned suppression of the immune response by antilymphocyte serum. *J. Immunol.* 130:2117–20
78. Bovbjerg, D., Ader, R., Cohen, N. 1984. Acquisition and extinction of conditioned suppression of a graft-vs-host response in the rat. *J. Immunol.* 132: 11–13
79. Cohen, N., Ader, R., Green, N., Bovbjerg, D. 1979. Conditioned suppression of a thymus-independent antibody response. *Psychosom. Med.* 41:487–91
80. Klosterhalfen, S., Klosterhalfen, W. 1987. Classically conditioned cyclophosphamide effects on white blood cell counts in rats. *Ann. NY Acad. Sci.* 496:569–77
81. Peeke, H. V. S., Ellman, G., Dark, K., Salfi, M., Reus, V. I. 1987. Cortisol and behaviorally conditioned histamine release. *Ann. NY Acad. Sci.* 496:583–87
82. McFarland, D., Hotchin, J. 1987. Animal models in behavioral neurovirology. In *Viruses, Immunity, and Mental Disorders*, ed. E. Kurstak, Z. J. Lipowski, P. V. Morozov, pp. 189–98. New York: Plenum
83. Lal, H., Forster, M. J. 1990. Brain reactive antibodies and learning. See Ref. 22
84. Schiffer, R. B., Hoffman, S. A. 1990. Behavioral sequelae of autoimmune disease. See Ref. 22
85. Ader, R., Grota, L. J., Moynihan, J. A., Cohen, N. 1990. Behavioral adaptations in autoimmune disease-susceptible mice. See Ref. 22
86. Ader, R., Grota, L. J., Cohen, N. 1987. Conditioning phenomena and immune function. *Ann. NY Acad. Sci.* 496:532–44
87. Crnic, L. 1990. Behavioral consequences of virus infection. See Ref. 22
88. Grota, L. J., Ader, R., Cohen, N. 1987. Taste aversion learning in autoimmune MrI-Ipr/Ipr and MrI +/+ mice. *Brain Behav. Immun.* 1:238–50
89. Grota, L. J., Schachtman, T. R., Moynihan, J. A., Cohen, N., Ader, R. 1989. Voluntary consumption of cyclophosphamide by MrI mice. *Brain Behav. Immun.* 3:263–73
90. Bost, L. K. 1988. Hormone and neuropeptide receptor on mononuclear leukocytes. *Prog. Allergy* 43:68–83
91. Pert, C. B., Ruff, M. R., Weber, R. J., Herkenham, M. 1985. Neuropeptides and their receptors: A psychosomatic network. *J. Immunol.* 135:820s–26s
92. Weigent, D. A., Blalock, J. E. 1987. Interactions between the neuroendocrine and immune systems: Common hormones and receptors. *Immunol. Rev.* 100:79–108
93. Blalock, J. E., Harbour-McMenamin, D., Smith, E. M. 1985. Peptide hormones shared by the neuroendocrine and immunologic systems. *J. Immunol.* 135: 858s–61s
94. Blalock, J. E. 1984. The immune system as a sensory organ. *J. Immunol.* 132:1067–70
95. Berkenbosch, J., van Oers, J., del Rey, A., Tilders, F., Besedovsky, H. 1987. Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. *Science* 238:524–26
96. Johnson, H. M., Torres, B. A. 1985. Regulation of lymphokine production by arginine vasopressin and oxytocin: Modulation of lymphocyte function by neurohypophyseal hormones. *J. Immunol.* 135:773s–75s
97. Berczi, I. 1986. The pituitary-thyroid axis. See Ref. 109, pp. 214–19
98. Maestroni, G. J. M. 1990. Role of the pineal neurohormone melatonin in the psycho-neuroendocrine-immune network. See Ref. 22
99. Berczi, I. 1986. The pituitary thyroid axis. See Ref. 109, pp. 185–212
100. Hall, N. R. S., O'Grady, M. P., Farah, J. R. Jr. 1990. Thymic hormones and immune function: Mediation via neuroendocrine circuits. See Ref. 22

101. Berczi, I., Nagy, E. 1990. Effect of hypophysectomy on immune function. See Ref. 22
102. Kelley, K. W. 1990. Growth hormone in immunobiology. See Ref. 22
103. Baroni, C. D., Fabris, N., Bertoli, G. 1969. Effects of hormones on development and function of lymphoid tissues: synergistic action of thyroxin and somatotrophic hormone in pituitary dwarf mice. *Immunology* 17:303–14
104. Comsa, J., Leonhardt, H., Schwarz, J. A. 1975. Influence of the thymus-corticotropin-growth hormone interaction on the rejection of skin allografts in the rat. *Ann. NY Acad. Sci.* 249:387–401
105. Berczi, I., Nagy, E., Asa, S. L., Kovacs, K. 1983. Pituitary hormones and contact sensitivity in rats. *Allergy* 38:325–30
106. Saxena, Q. B., Saxena, R. K., Adler, W. H. 1982. Regulation of natural killer activity in vivo. III. Effect of hypophysectomy and growth hormone treatment on the natural killer activity of the mouse spleen cell population. *Int. Arch. Allergy Appl. Immunol.* 67:169–74
107. Pandian, M. R., Talwar, G. P. 1971. Effect of growth hormone on the metabolism of thymus and on the immune response against sheep erythrocytes. *J. Exp. Med.* 134:1095–113
108. Nagy, E., Berczi, I., Friesen, H. G. 1983. Regulation of immunity in rats by lactogenic and growth hormones. *Acta Endocrinol.* 102:351–57
109. Berczi, I., ed. 1986. *Pituitary Function and Immunity*. Boca Raton: CRC Press
110. Kelley, K. W., Brief, S., Westly, H. J., Novakofski, J., Bechtel, P. J., et al. 1986. GH3 pituitary adenoma cells can reverse thymic aging in rats. *Proc. Natl. Acad. Sci. USA* 83:5663–67
111. Davila, D. R., Brief, S., Simon, J., Hammer, R. E., Brinster, R. L., Kelley, K. W. 1987. Role of growth hormone in regulating T-dependent immune events in aged, nude, and transgenic rodents. *J. Neurosci. Res.* 18:108–16
112. Mercola, K. E., Cline, M. J., Colde, D. W. 1981. Growth hormone stimulation of normal and leukemic human T lymphocyte proliferation in vitro. *Blood* 58:337–40
113. Kiess, W., Holtmann, H., Butendadt, O., Eife, R. 1983. Modulation of lymphoproliferation by human growth hormone. *Eur. J. Pediatr.* 140:47–50
114. Snow, E. C., Feldbush, T. L., Oaks, J. A. 1981. The effect of growth hormone and insulin upon MLC responses and generation of cytotoxic T lymphocytes. *J. Immunol.* 126:161–64
115. Edwards, C. K. III, Ghiasuddin, S. M., Schepper, J. M., Yunger, L. M., Kelley, K. W. 1988. A newly defined property of somatotropin: priming of macrophages for production of superoxide anion. *Science* 239:769–71
116. Kelley, K. W. 1989. Growth hormone, lymphocytes and macrophages. *Biochem. Pharmacol.* 38:705–13
117. Bunner, D. L., Morris, E., Smallridge, R. C. 1984. Circadian growth hormone and prolactin blood concentration during a self-limited viral infection and artificial hyperthermia in man. *Metabolism* 33:337–41
118. Kasting, N. W., Martin, J. B. 1982. Altered release of growth hormone and thyrotropin induced by endotoxin in the rat. *Am. J. Physiol.* 243:332–37
119. Rettori, V., Jurcovicova, J., McCann, S. M. 1987. Control action of interleukin-1 in altering the release of TSH, growth hormone, and prolactin in the male rat. *J. Neurosci. Res.* 18:179–83
120. Weigent, D. A., Baxter, J. B., Wear, W. E., Smith, L. R. Bost, K. L., Blalock, J. E. 1988. Production of immunoreactive growth hormone by mononuclear leukocytes. *FASEB J.* 2:2812–18
121. Spangelo, B. L., Hall, N. R., Dunn, A. J., Goldstein, A. L. 1987. Thymosin fraction 5 stimulates the release of prolactin from cultured GH3 cells. *Life Sci.* 40:283–88
122. Cross, R. J., Markesbery, W. R., Brooks, W. H., Roszman, T. L. 1984. Hypothalamic-immune interactions: Neuromodulation of natural killer activity by lesioning of the anterior hypothalamus. *Immunology* 51:399–405
123. Cross, R. J., Brooks, W. H., Roszman, T. L. 1987. Modulation of T-suppressor cell activity by central nervous system catecholamine depletion. *J. Neurosci. Res.* 18:75–81
124. Bernton, E. W., Bryant, H. U., Holaday, J. W. 1990. Prolactin and immune function. See Ref. 22
125. Nagy, E., Berczi, I., Wren, G. E., Asa, S. A., Kovacs, K. 1983. Immunomodulation by bromocriptine. *Immunopharmacology* 67:231–43
126. Bernton, E. W., Meltzer, M. T., Holaday, J. W. 1988. Suppression of macrophage activation and T-lymphocyte function in hypoprolactinemic mice. *Science* 239:401–4
127. Bryant, H. U., Bernton, E. W., Hola-

day, J. W. 1989. Cysteamine produces dose-related biphasic immunomodulatory effects in mice. *J. Pharmacol. Exp. Ther.* 249:424–29

128. Hartman, D., Holaday, J. W., Bernton, E. W. 1989. Inhibition of lymphocyte proliferation by antibodies to PRL. *FASEB J.* 3:2194–201
129. Demarest, K. T., Riegle, G. D., Moore, K. E. 1985. The interrelationship between the rapid "tonic" and the delayed "induction" components of the prolactin-induced activation of tuberoinfundibular dopamine neurons. In *Prolactin. Basic and Clinical Correlates*, ed. R. M. MacLeod, U. Scapaginini, M. O. Thorner, pp. 533–42. New York: Springer-Verlag
130. Gilbeau, P. M., Almirez, R. G., Holaday, J. W., Smith, C. G. 1985. Opioid effects on plasma concentrations of leutenizing hormone and prolactin in the adult male rhesus monkey. *J. Clin. Endocrinol. Metab.* 60:299–305
131. Montgomery, D. W., Zukoski, C. F., Shah, G. N., Buckley, A. R., Pacholczyk, T., Russell, D. H. 1987. Concanavalin A-stimulated murine splenocytes produce a factor with prolactin-like bioactivity and immunoreactivity. *Biochem. Biophys. Res. Commun.* 145: 692–98
132. DiMattia, G. E., Gellersen, B., Bohnet, H. G., Friesen, H. G. 1988. A human-B-lymphoblastoid cell-line produces prolactin. *Endocrinology* 122:2508–17
133. Bernton, E. W., Beach, J. E., Holaday, J. W., Smallridge, R. C., Fein, H. G. 1987. Release of multiple hormones by a direct action of interleukin-1 on pituitary cells. *Science* 238:519–21
134. Moore, K. E., Riegle, G. D., Demerest, K. T. 1985. Effects of long-term treatment with estradiol and haloperidol on serum concentrations of prolactin and tuberoinfundibular dopaminergic neuronal activity. In *Prolactin—Basic and Clinical Correlates*, ed. R. M. MacLeod, U. Scapaginini, M. O. Thorner, pp. 543–49. New York:Springer-Verlag
135. Copinschi, G., L'Hermite, M., Leclercq, R. 1975. Effects of glucocorticoids on pituitary hormonal response to hypoglycemia. Inhibition of prolactin release. *J. Clin. Endocrinol. Metab.* 40:442–49
136. Tache, Y., Du Ruisseau, P., Ducharme, J. R., Collu, R. 1978. Pattern of adenohypophyseal hormone change in male rats following chronic stress. *Neuroendocrinology* 26:208–19
137. Lundblad, J. R., Roberts, J. L. 1989. Regulation of proopiomelanocortin gene expression in pituitary. *Endocr. Rev.* 9:136–58
138. Evans, C. J., Erdelyi, E., Barchas, J. D. 1986. Candidate opioid peptides for interaction with the immune system. In *Enkephalins and Endorphins*, ed. N. P. Plotnikoff, R. E. Faith, A. J. Murgo, R. A. Good, pp. 3–16. New York: Plenum
139. Smith, E. M., Morrill, A. C., Meyer, W. J., Blalock, J. E. 1986. Corticotropin releasing factor induction of leukocyte-derived immunoreactive ACTH and endorphins. *Nature* 321:881–82
140. Heijnen, C. J., Kavelaars, A., Ballieux, R. E. 1990. CRH and POMC-derived peptides in the modulation of immune function. See Ref. 22
141. Kavelaars, A., Ballieux, R. E., Heijnen, C. J. 1989. The role of interleukin-1 in the CRH- and AVP-induced secretion of ir-β-endorphin by human peripheral blood mononuclear cells. *J. Immunol.* 142:2338–42
142. Berczi, I. 1986. The influence of pituitary-adrenal axis on the immune system. See Ref. 109, pp. 49–132
143. Johnson, H. M., Smith, E. M., Torres, B. A., Blalock, J. E. 1982. Regulation of the in vitro antibody response by neuroendocrine hormones. *Proc. Natl. Acad. Sci. USA* 79:4171–74
144. Koff, W. C., Dunegan, M. A. 1985. Modulation of macrophage-mediated tumoricidal activity by neuropeptides and neurohormones. *J. Immunol.* 135: 350–54
145. Alvarez-Mon, M., Kehrl, J. H., Fauci, A. S. 1985. A potential role for adrenocorticotropin in regulating human B lymphocyte functions. *J. Immunol.* 135: 3823–26
146. Johnson, H. M., Torres, B. A., Smith, E. M., Dion, L. D., Blalock, J. E. 1984. Regulation of lymphokine (gamma-interferon) production by corticotropin. *J. Immunol.* 132:246–50
147. Fontana, L., Fattorossi, A., D'Amelio, R., Miglioratie, A., Perricone, R. 1987. Modulation of human concanavalin A-induced lymphocyte proliferative response by physiological concentrations of β-endorphin. *Immunopharmacology* 13:111–15
148. Gilman, S. C., Schwartz, J. M., Milner, R. J., Bloom, F. E., Feldman, J. D. 1982. β-Endorphin enhances lymphocyte proliferative responses. *Proc. Natl. Acad. Sci. USA* 79:4226–30
149. Kayu, N., Allen, J., Morley, U. J. E. 1984. Endorphins stimulate normal human peripheral blood lymphocyte natural killer activity. *Life Sci.* 35:53–59

150. Froelich, C. J., Bankhurst, A. D. 1984. The effect of B-endorphin on natural cytotoxicity and antibody dependent cellular cytotoxicity. *Life Sci.* 35:261–65
151. Heijnen, C. J., Bevers, C., Kavelaars, A., Ballieux, R. E. 1985. Effect of alpha endorphin on the antigen-induced primary antibody response of human blood B cells in vitro. *J. Immunol.* 136:213–16
152. Brown, S. L., Van Epps, D. E. 1986. Opioid peptides modulate production of interferon gamma by human mononuclear cells. *Cell. Immunol.* 103:19–26
153. Van Epps, D. E., Saland, L. 1984. Beta-endorphin and met-enkephalin stimulate human peripheral-blood mononuclear cell chemotaxis. *J. Immunol.* 132:3046–53
154. Sibinga, N. E. S., Goldstein, A. 1988. Opioid peptides and opioid receptors in cells of the immune system. *Annu. Rev. Immunol.* 6:219–49
155. Carr, D. J. 1988. Opioid receptors on cells of the immune system. *Prog. NeuroEndocrinImmun.* 1:8–14
156. Claas, F. H. J., van Ree, J. M., Verhoeven, W. M. A., van der Poel, J. J., Verduyn, W., et al. 1986. The interaction between gamma-type endorphins and HLA class-I antigens. *Hum. Immunol.* 15:347–56
157. Murgo, A. J., Faith, R. E., Plotnikoff, N. P. 1986. Enkephalins: Mediators of stress-induced immunomodulation. See Ref. 138, pp. 221–39
158. Wybran, J. 1986. Enkephalins as molecules of lymphocyte activation and modifiers of the biological response. See Ref. 138, pp. 253–82
159. Lewis, J. W., Shavit, Y., Martin, F. C., Terman, G. W., Gale, R. P., Liebeskind, J. C. 1986. Effects of stress and morphine on natural killer cell activity and on mammary tumor development. See Ref. 138, pp. 101–8
160. Cupps, T. R., Fauci, A. S. 1982. Corticosteroid-mediated immunoregulation in man. *Immunol. Rev.* 65:133–55
161. Munck, A., Guyre, P. M., Holbrook, N. J. 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr. Rev.* 5:25–44
162. Munck, A., Guyre, P. M. 1986. Glucocorticoid physiology, pharmacology and stress. In *Steroid Hormone Resistance*, ed. G. P. Chrousos, D. L. Loriaux, M. B. Lipsett, pp. 81–96. New York: Plenum
163. Munck, A., Guyre, P. M. 1990. Glucocorticoids and immune function. See Ref. 22
164. Besedovsky, H. O., Sorkin, E., Keller, M., Müller, J. 1975. Changes in blood hormone levels during the immune response. *Proc. Soc. Exp. Biol. Med.* 150:466–70
165. Besedovsky, H. O., del Rey, A., Sorkin, E. 1981. Lymphokine-containing supernatants from Con A-stimulated cells increase corticosterone blood levels. *J. Immunol.* 126:385–87
166. Besedovsky, H. O., Sorkin, E. 1977. Network of immune neuroendocrine interactions. *J. Clin. Exp. Immunol.* 27:1–12
167. Besedovsky, H. O., del Rey, A., Sorkin, E. 1979. Antigenic competition between horse and sheep red blood cells as hormone-dependent phenomenon. *Clin. Exp. Immunol.* 37:106–13
168. del Rey, A., Besedovsky, H., Sorkin, E. 1984. Endogenous blood levels of corticosterone control the immunological cell mass and B-cell activity in mice. *J. Immunol.* 133:572–75
169. Berardini, R., Scapaginini, U. 1988. Interactions between cytokines and the hypothalamic-pituitary-adrenal axis. *Prog. NeuroEndocrinImmunol.* 1:13–15
170. Sapolsky, R., Rivier, C., Yamamoto, G., Plotsky, P., Vale, W. 1987. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science* 238:522–24
171. Besedovsky, H. O., del Rey, A., Sorkin, E., Dinarello, C. A. 1986. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science* 233:652–54
172. Knudsen, P. J., Dinarello, C. A., Strom, T. B. 1987. Glucocorticoids inhibit transcriptional and post-transcriptional expression of interleukin-1 in U937 cells. *J. Immunol.* 139:4129–34
173. Kern, J. A., Lamb, R. J., Reed, J. C., Daniele, R. P., Nowell, P. C. 1988. Dexamethasone inhibition of interleukin-1 beta-production by human-monocytes: posttranscriptional mechanisms. *J. Clin. Invest.* 81:237–44
174. Lew, W., Oppenheim, J. J., Matsushima, K. 1988. Analysis of the suppression of IL-1-alpha and IL-1-beta production in human peripheral blood mononuclear adherent cells by a glucocorticoid hormone. *J. Immunol.* 140:1895–02
175. Beutler, B., Cerami, A. 1988. Cachetin (tumor necrosis factor): A macrophage hormone governing cellular metabolism

and inflammatory response. *Endocr. Rev.* 9:57–66
176. Arya, S. K., Wong-Staal, F., Gallo, R. C. 1984. Dexamethasone-mediated inhibition of human T cell growth factor in gamma-interferon messenger RNA. *J. Immunol.* 133:273–76
177. Grabstein, K., Dower, S., Gillis, S., Urdal, D., Larsen, A. 1986. Expression of interleukin 2, interferon gamma and the IL-2 receptor by human peripheral blood lymphocytes. *J. Immunol.* 136: 4503–8
178. Gessani, S., McCandless, S., Baglioni, C. 1988. The glucocorticoid dexamethasone inhibits synthesis of interferon by decreasing the level of its mRNA. *J. Biochem.* 263:7454–57
179. Culpepper, J. A., Lee, F. 1985. Regulation of IL-3 expression by glucocorticoids in cloned murine T lymphocytes. *J. Immunol.* 135:3191–97
180. Holbrook, N. J., Cox, W. I., Horner, H. C. 1983. Direct suppression of natural killer activity in human peripheral blood leukocyte cultures by glucocorticoids and its modulation by interferon. *Cancer Res.* 43:4019–25
181. Felten, D. L., Felten, S. Y., Carlson, S. L., Olschowka, J. A., Livnat, S. 1985. Noradrenergic and peptidergic innervation of lymphoid tissue. *J. Immunol.* 135:755s–65s
182. Livnat, S., Felten, S. Y., Carlson, S. L., Bellinger, D. L., Felten, D. L. 1985. Involvement of peripheral and central catecholamine systems in neural-immune interactions. *J. Neuroimmunol.* 10:5–30
183. Berczi, I., Nagy, E., Kovacs, K., Horvath, E. 1981. Regulation of humoral immunity in rats by pituitary hormones. *Acta Endocrinol.* 98:506–13
184. Felten, S. Y., Felten, D. L., Bellinger, D. L., Carlson, S. L., Ackerman, K. D., et al. 1988. Noradrenergic sympathetic innervation of lymphoid organs. *Prog. Allergy* 43:14–36
185. Felten, S. Y., Olschowka, J. A., Ackerman, K. D., Felten, D. L. 1988. Catecholaminergic innervation of the spleen: Are lymphocytes targets of noradrenergic nerves? In *Progress in Catecholamine Research, Part A: Basic Aspects and Peripheral Mechanisms,* ed. A. Dahlström, R. H. Belmaker, M. Sandler, pp. 525–31. New York: Liss
186. Felten, D. L., Felten, S. Y., Bellinger, D. L., Carlson, S. L., Ackerman, K. D., et al. 1987. Noradrenergic sympathetic neural interactions with the immune system: structure and function. *Immunol. Rev.* 100:225–60
187. Ackerman, K. D., Bellinger, D. L., Felten, S. Y., Felten, D. L. 1990. Ontogeny and senescence of noradrenergic innervation of the rodent thymus and spleen. See Ref. 22
188. Felten, S. Y., Olschowka, J. A. 1987. Noradrenergic sympathetic innervation of the spleen: II. Tyrosine hydroxylase (TH)-positive nerve terminals form synaptic-like contacts on lymphocytes in the splenic white pulp. *J. Neurosci. Res.* 18:37–48
189. Felten, D. L., Felten, S. Y., Carlson, S. L., Bellinger, D. L., Ackerman, K. D., Romano, T. A., Livnat, S. 1988. Development, aging, and plasticity of noradrenergic sympathetic innervation of secondary lymphoid organs: Implications for neural immune interactions. See Ref. 185, pp. 517–24
190. Felten, D. L., Felten, S. Y., Madden, K. S., Ackerman, K. D., Bellinger, D. L. 1989. Development, maturation and senescence of sympathetic innervation of secondary immune organds. In *Development, Maturation, and Senescence of Neuroendocrine Systems,* ed. M. P. Schreibman, C. G. Scanes, pp. 381–96 New York: Academic
191. Felten, S. Y., Felten, D. L. 1989. The innervation of lymphoid organs. See Ref. 22
192. Calvo, W. 1968. The innervation of the bone marrow in laboratory animals. *Am. J. Anat.* 123:315–28
193. DePace, D. M., Webber, R. H. 1975. Electrostimulation and morphologic study of the nerves to the bone marrow of the albino rat. *Acta Anat.* 93:1–18
194. Lichtman, M. A. 1981. The ultrastructure of the hemopoietic environment of the marrow: A review. *Exp. Hematol.* 9:391–410
195. Slotkin, T. A., Lau, C., Kavlock, R. J., Gray, J. A., Orband-Miller, L., et al. 1989. Role of sympathetic neurons in biochemical and functional development of the kidney: Neonatal sympathectomy with 6-hydroxydopamine. *J. Pharmacol. Exp. Ther.* In press
196. Miller, M. L., McCuskey, R. S. 1973. Innervation of bone marrow in the rabbit. *Scand. J. Haematol.* 10:17–23
197. Webber, R. H., DeFelice, R., Ferguson, R. J., Powell, J. P. 1970. Bone marrow response to stimulation of the sympathetic trunks in rats. *Acta Anat.* 77:92–97
198. Byron, J. W. 1972. Evidence for a beta adrenergic receptor initiating DNA syn-

thesis in haemopoietic stem cells. *Exp. Cell. Res.* 71:228–32

199. Bellinger, D. L., Felten, S. Y., Felten, D. L. 1988. Maintenance of noradrenergic sympathetic innervation in the involuted thymus of the aged Fischer 344 rat. *Brain Behav. Immun.* 2:133–50
200. Williams, J. M., Felten, D. L. 1981. Sympathetic innervation of murine thymus and spleen: A comparative histofluorescence study. *Anat. Rec.* 199:531–42
201. Williams, J. M., Peterson, R. G., Shea, P. A., Schmedtje, J. F., Bauer, D. C., Felten, D. L. 1981. Sympathetic innervation of murine thymus and spleen: Evidence for a functional link between the nervous and immune systems. *Brain Res. Bull.* 6:83–94
202. Bulloch, K., Pomerantz, W. 1984. Autonomic nervous system innervation of thymic related lymphoid tissue in wild-type and nude mice. *J. Comp. Neurol.* 228:57–68
203. Bulloch, K., Moore, R. Y. 1981. Innervation of the thymus gland by brain stem and spinal cord in mouse and rat. *Am. J. Anat.* 162:157–66
204. Fujiwara, M., Muryobayashi, T., Shimamoto, K. 1966. Histochemical demonstration of monoamines in the thymus of rats. *Jpn. J. Pharmacol.* 16:493–94
205. Sergeeva, V. E. 1974. Histotopography of catecholamines in the mammalian thymus. *Bull. Exp. Biol. Med.* 77:456–58
206. Nance, D. M., Hopkins, D. A., Biegler, D. 1987. Re-investigation of the innervation of the thymus gland in mice and rats. *Brain Behav. Immun.* 1: 134–47
207. Singh, U. 1979. Effect of catecholamines on lymphopoiesis in fetal mouse thymic explants. *Eur. J. Immunol.* 14: 757–59
208. Singh, U. 1979. Effect of catecholamines on lymphopoiesis in fetal mouse thymic explants. *J. Anat.* 129:279–92
209. Singh, U., Millson, S., Smith, P. A., ●wen, J. J. T. 1979. Identification of β adrenoceptors during thymocyte ontogeny in mice. *Eur. J. Immunol.* 9:31–35
210. Singh, U., Owen, J. J. T. 1975. Studies on the effect of various agents on the maturation of thymus stem cells. *Eur. J. Immunol.* 5:286–88
211. Singh, U. 1985. Lymphopoiesis in the nude fetal mouse thymus following sympathectomy. *Cell. Immunol.* 93:222–28
212. Livnat, S., Madden, K. S., Felten, D. L., Felten, S. Y. 1987. Regulation of the immune system by sympathetic neural mechanisms. *Prog. Neuro-psychopharmacol. Biol. Psychiatry* 11:145–52
213. Strom, T. B., Lane, M. A., George, K. 1981. The parallel, time-dependent, bimodal change in lymphocyte cholinergic binding activity and cholinergic influence upon lymphocyte-mediated cytotoxicity after lymphocyte activation. *J. Immunol.* 127:705–10
214. Strom, T. B., Sytkowski, A. J., Carpenter, C. B., Merrill, J. P. 1974. Cholinergic augmentation of lymphocyte-mediated cytotoxicity. A study of the cholinergic receptor of cytotoxic T lymphocytes. *Proc. Natl. Acad. Sci. USA* 71:1330–33
215. Maslinski, W., Kullberg, M., Nordström, O., Bartfai, T. 1988. Muscarinic receptors and receptor-mediated actions on rat thymocytes. *J. Neuroimmunol.* 17:265–74
216. Maslinski, W., Krzystynaik, K., Grabczewska, E., Ryzewski, J. 1983. Muscarinic acetylcholine receptors of rat lymphocytes. *Biochim. Biophys. Acta* 758:93–97
217. Felten, D. L., Felten, S. Y. 1989. Innervation of the thymus. In *Thymus Update*, ed. M. D. Kendall, M. A. Ritter, pp. 73–88. London: Harwood Academic
218. Geenen, V., Legros, J.-J., Franchimont, P., Defresne, M. P., Boniver, J., et al. 1987. The thymus as a neuroendocrine organ: Synthesis of vasopressin and oxyto-in in human thymic epithelium. *Ann. NY Acad. Sci.* 496:56–66
219. Geenen, V., Legros, J.-J., Franchimont, P., Baudrihaye, M., Defresne, M. P., Boniver, J. 1986. The neuroendocrine thymus: Coexistence of oxytocin and neurophysin in the human thymus. *Science* 232:508–10
220. Markwick, A. J., Lolait, S. J., Funder, J. W. 1986. Immunoreactive arginine vasopressin in the rat thymus. *Endocrinology* 119:1690–96
221. Clements,, J. A., Funder, J. W. 1986. Arginine vasopressin (AVP) and AVP-like immunoreactivity in peripheral tissues. *Endocr. Rev.* 7:449–60
222. Weihe, E., Müller, S., Fink, T., Zentel, H. J. 1989. Tachykinins, calcitonin gene-related peptide and neuropeptide Y in nerves of the mammalian thymus: interactions with mast cells in autonomic and sensory neuroimmunomodulation. *Neurosci. Lett.* 100:77–82
223. Felten, S. Y., Lorton, D., Felten, D. L. 1989. Substance P (SP) innervation of

the rat thymus. *Soc. Neurosci. Abstr.* 15:714

224. Bellinger, D. L., Felten, S. Y., Lorton, D., Felten, D. L. 1989. Origin of noradrenergic innervation of the spleen in rats. *Brain Behav. Immun.* 3: In press
225. Ackerman, K. D., Felten, S. Y., Bellinger, D. L., Felten, D. L. 1987. Noradrenergic sympathetic innervation of the spleen: III. Development of innervation in the rat spleen. *J. Neurosci. Res.* 18:49–54
226. Ackerman, K. D., Felten, S. Y., Bellinger, D. L., Livnat, S., Felten, D. L. 1987. Noradrenergic sympathetic innervation of spleen and lymph nodes in relation to specific cellular compartments. In *Progress in Immunology IV*, ed. B. Cinader, R. G. Miller, pp. 588–600. Orlando, FL: Academic
227. Ackerman, K. D., Felten, S. Y., Dijkstra, C. D., Livnat, S., Felten, D. L. 1989. Parallel development of noradrenergic innervation and cellular compartmentation in the rat spleen. *Exp. Neurol.* 103:239–55
228. Felten, D. L., Ackerman, K. D., Wiegand, S. J., Felten, S. Y. 1987. Noradrenergic sympathetic innervation of the spleen: I. Nerve fibers associate with lymphocytes and macrophages in specific compartments of the splenic white pulp. *J. Neurosci. Res.* 18:28–36
229. Lorton, D., Bellinger, D. L., Felten, S. Y., Felten, D. L. 1989. Substance P (SP) and calcitonin gene-related peptide (CGRP) innervation of the rat spleen. *Soc. Neurosci. Abstr.* 15:714
230. Romano, T. A., Olschowka, J. A., Felten, S. Y., Felten, D. L. 1989. Neuropeptide-Y involvement in neural-immune interactions in the rat spleen. *Soc. Neurosci. Abstr.* 15:714
231. Garcia, J., Hankins, W. G., Rusiniak, K. W. 1974. Behavioral regulation of the milieu interne in man and rat. *Science* 185:824–31
232. Fried, G., Terenius, L., Brodin, E., Efendic, S., Dockray, G., et al. 1986. Neuropeptide Y, enkephalin and noradrenaline coexist in sympathetic neurons innervating the bovine spleen. Biochemical and immunohistochemical evidence. *Cell Tissue Res.* 243:495–508
233. Lundberg, J. M., Ånggård, A., Pernow, J., Hökfelt, T. 1985. Neuropeptide, Y-, substance P- and VIP-immunoreactive nerves in cat spleen in relation to autonomic vascular and volume control. *Cell Tissue Res.* 239:9–18
234. Schultzberg, M., Svenson, S. B., Unden, A., Bartfai, T. 1987. Interleukin-1-like immunoreactivity in peripheral tissues. *J. Neurosci. Res.* 18:184–89
235. Felten, D. L., Livnat, S., Felten, S. Y., Carlson, S. L., Bellinger, D. L., Yeh, P. 1984. Sympathetic innervation of lymph nodes in mice. *Brain Res. Bull.* 13:693–99
236. Giron, L. T., Crutcher, K. A., Davis, J. N. 1980. Lymph nodes—a possible site for sympathetic neuronal regulation of immune responses. *Ann. Neurol.* 8:520–25
237. Felten, D. L., Overhage, J. M., Felten, S. Y., Schmedtje, J. F. 1981. Noradrenergic sympathetic innervation of lymphoid tissue in the rabbit appendix: further evidence for a link between the nervous and immune systems. *Brain Res. Bull.* 7:595–612
238. Jesseph, J. M., Felten, D. L. 1984. Noradrenergic innervation of the gut-associated lymphoid tissues (GALT) in the rabbit. *Anat. Rec.* 208:81A
239. McFarland, D. J., Hotchin, J. 1984. Behavioral sequelae to early postnatal cytomegalovirus infection in mice. *Physiol. Behav.* 12:45–47
240. Ottaway, C. A., Lewis, D. L., Asa, S. L. 1987. Vasoactive intestinal peptide-containing nerves in Peyer's patches. *Brain Behav. Immun.* 1:148–58
241. Ottaway, C. A., Bernaerts, C., Chan, B., Greenberg, G. R. 1983. Specific binding of vasoactive intestinal peptide to human circulating mononuclear cells. *Can. J. Physiol. Pharmacol.* 61:664–71
242. Ottaway, C. A., Greenberg, G. R. 1984. Interaction of vasoactive intestinal peptide with mouse lymphocytes: Specific binding and the modulation of mitogen responses. *J. Immunol.* 132: 417–23
243. Ottaway, C. A. 1984. In vitro alteration of receptors for vasoactive intestinal peptide changes the in vivo localization of mouse T cells. *J. Exp. Med.* 160: 1054–69
244. Ottaway, C. A. 1985. Evidence for local neuromodulation of T cell migration in vivo. *Adv. Exp. Med.* 186:637–45
245. Stead, R. H., Tomioka, M., Quinonez, G., Simon, G. T., Felten, S. Y., Bienenstock, J. 1987. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. *Proc. Natl. Acad. Sci. USA* 84:2975–79
246. Felten, S. Y., Housel, J., Felten, D. L. 1986. Use of in vivo dialysis for evaluation of splenic norepinephrine and serotonin. *Soc. Neurosci. Abstr.* 12:1065
247. Bidart, J. M., Motte, Ph., Assicot, M.,

Bohuon, C., Bellet, D. 1983. Catechol-O-methyltransferase activity and aminergic binding sites distribution in human peripheral blood lymphocyte subpopulations. *Clin. Immunol. Immunopathol.* 26:1–9

248. Bishopric, N. H., Cohen, H. J., Lefkowitz, R. J. 1980. Beta adrenergic receptors in lymphocyte subpopulations. *J. Allergy Clin. Immunol.* 65:29–33
249. Hadden, J. W., Hadden, E. M., Middleton, E. Jr. 1970. Lymphocyte blast transformation. I. Demonstration of adrenergic receptors in human peripheral lymphocytes. *Cell. Immunol.* 1:583–95
250. Hadden, J. W. 1977. Cyclic nucleotides in lymphatic proliferation and differentiation. In *Immunopharmacology,* ed. J. W. Hadden, R. C. Caffey, F. Spreafico, pp. 1–28. New York: Plenum
251. Moore, R. D., Mumaw, V. R., Schoenberg, M. C. 1964. The structure of the spleen and its functional implications. *Exp. Mol. Pathol.* 3:31–50
252. Loveland, B. E., Jarrott, B., McKenzie, I. F. C. 1981. The detection of beta adrenoceptors on murine lymphocytes. *Int. J. Immunopharmacol.* 3:45–55
253. Miles, K., Atweh, S., Otten, G., G., Arnason, B. G. W., Chelmicka-Schorr, E. 1984. Beta-adrenergic receptors on splenic lymphocytes from axotomized mice. *Int. J. Immunopharmacol.* 6:171–77
254. Pochet, R., Delespesse, G. 1983. β-Adrenoreceptors display different efficiency on lymphocyte subpopulations. *Biochem. Pharmacol.* 32:1651–55
255. Pochet, R., Delespesse, G., Gausset, P. W., Collet, H. 1979. Distribution of beta-adrenergic receptors on human lymphocyte subpopulations. *Clin. Exp. Immunol.* 38:578–84
256. Bannister, R., Boylston, A. W., Davies, I. B., Mathias, C. J., Sever, P. S., Suderam, D. 1981. Beta-receptor numbers and thermodynamics in denervation supersensitivity. *J. Physiol.* 319:369–77
257. Williams, L. T., Snyderman, R., Lefkowitz, R. J. 1976. Identification of β-adrenergic receptors in human lymphocytes by (—)[3H]-alprenolol binding. *J. Clin. Invest.* 57:149–55
258. Fuchs, B. A., Albright, J. W., Albright, J. F. 1988. β-adrenergic receptors on murine lymphocytes: Density varies with cell maturity and lymphocyte subtype and is decreased after antigen administration. *Cell. Immunol.* 144:231–45
259. Sanders, V. M., Munson, A. E. 1985. Role of alpha adrenoceptor activation in modulating the murine primary antibody response in vitro. *J. Pharmacol. Exp. Ther.* 232:395–400
260. Scarpace, P. J., Abrass, I. B. 1982. Desensitization of adenylate cyclase and down regulation of beta-adrenergic receptors after in vivo administration of beta-agonist. *J. Pharmacol. Exp. Ther.* 223:327–31
261. Beckner, S. K., Farrar, W. L. 1988. Potentiation of lymphokine-activated killer cell differentiation and lymphocyte proliferation by stimulation of protein kinase C or inhibition of adenylate cyclase. *J. Immunol.* 140:208–14
262. O'Dorisio, M. S., Wood, C. L., O'Dorisio, T. M. 1985. Vasoactive intestinal peptide and neuropeptide modulation of the immune response. *J. Immunol.* 135:792s–96s
263. O'Dorisio, M. S., Hermina, N. S., O'Dorisio, T. M., Balcerzak, S. P. 1981. Vasoactive intestinal polypeptide modulation of lymphocyte adenylate cyclase. *J. Immunol.* 127:2551–54
264. Payan, D. G., Brewster, D. R., Goetzl, E. J. 1984. Stereospecific receptors for substance P on cultured human IM-9 lymphoblasts. *J. Immunol.* 133:3260–65
265. Payan, D. G., Brewster, D. R., Goetzl, E. J. 1983. Specific stimulation of human T lymphocytes by substance P. *J. Immunol.* 131:1613–15
266. McGillis, J. P., Organist, M. L., Payan, D. G. 1987. Substance P and immunoregulation. *Fed. Proc.* 46:196–99
267. Jackson, J. C., Walker, R. F., Brooks, W. H., Roszman, T. L. 1988. Specific uptake of serotonin by murine macrophages. *Life Sci.* 42:1641–50.
268. Williams, W. R., Davies, B. H. 1985. Modulation of lymphocyte adrenergic receptors by hormones and anti-asthmatic drugs. *J. Clin. Lab. Immunol.* 16:131–36
269. De Blasi, A., Lipartiti, M., Algeri, S., Sacchetti, G., Costantini, C., et al. 1986. Stress induced desensitization of lymphocyte β-adrenoceptors in young and aged rats. *Pharmacol. Biochem. Behav.* 24:991–98
270. Hui, K. K. P., Conolly, M. E., Tashkin, D. P. 1982. Reversal of human lymphocyte β-adrenoceptor desensitization by glucocorticoids. *Clin. Pharmacol. Ther.* 32:566–71
271. Brodde, O.-E., Brinkmann, M., Schemuth, R., O'Hara, N., Daul, A. 1985. Terbutaline-induced desensitization of human lymphocyte β-2-adrenoceptors. Accelerated restoration of β-adrenoceptor responsiveness of predni-

sone and ketotifen. *J. Clin. Invest.* 76:1096–101
272. Brodde, O. E. 1983. Endogenous and exogenous regulation of human alpha- and beta-adrenergic receptors. *J. Recept. Res.* 3:151–62
273. Cotecchia, S., De Blasi, A. 1984. Glucocorticoids increase β-adrenoceptors on human intact lymphocytes in vitro. *Life Sci.* 35:2359–64
274. Madden, K. S., Felten, S. Y., Felten, D. L., Livnat, S. 1989. Sympathetic neural modulation of the immune system. I. Depression of T cell immunity in vivo and in vitro following chemical sympathectomy. *Brain Behav. Immun.* 3:72–89
275. Singh, U., Owen, J. J. T. 1976. Studies on the maturation of thymus stem cells—The effects of catecholamines, histamine, and peptide hormones on the expression of T alloantigens. *Eur. J. Immunol.* 6:59–62
276. Johnson, D. L., Ashmore, R. C., Gordon, M. A. 1981. Effects of beta-adrenergic agents on the murine lymphocyte response to mitogen stimulation. *J. Immunopharmacol.* 3:205–19
277. Hadden, J. W. 1977. Cyclic nucleotides in lymphocyte proliferation and differentiation. In *Immunopharmacology,* ed. J. W. Hadden, R. G. Coffey, F. Spreafico, pp. 1–28. New York: Plenum
278. Sanders, V. M., McCall, C. O., Horsman, D. A. 1985. Kinetics of the alpha-2 adrenoceptor-induced inhibition of the primary antibody response in vitro. *Fed. Proc.* 44:1488
279. Sanders, V. M., Munson, A. E. 1984. Beta adrenoceptor mediation of the enhancing effect of norepinephrine on the murine primary antibody response in vitro. *J. Pharmacol. Exp. Ther.* 230: 183–92
280. Sanders, V. M., Munson, A. E. 1984. Kinetics of the enhancing effect produced by norepinephrine and terbutaline on the murine primary antibody response in vitro. *J. Pharmacol. Exp. Ther.* 231:527–31
281. Sanders, V. M., Munson, A. E. 1985. Norepinephrine and the antibody response. *Pharmacol. Rev.* 37:229–48
282. Snow, E. C. 1985. Insulin and growth hormone as minor growth factors that potentiate lymphocyte activation. *J. Immunol.* 135:776s–78s
283. Livnat, S., Eisen, J., Felten, D. L., Felten, S. Y., Irwin, J., Madden, K. S., Sundaresan, P. J. 1988. Behavioral and sympathetic neural modulation of immune function. See Ref. 185, pp. 539–46
284. Lappin, D., Whaley, K. 1982. Adrenergic receptors on monocytes modulate complement component synthesis. *Clin. Exp. Immunol.* 47: 606–12
285. Ernström, U., Sandberg, G. 1973. Effects of adrenergic alpha- and beta-receptor stimulation on the release of lymphocytes and granulocytes from the spleen. *Scand. J. Haematol.* 11:275–86
286. Ernström, U., Söder, O. 1975. Influence of adrenaline on the dissemination of antibody-producing cells from the spleen. *Clin. Exp. Immunol.* 21:131–40
287. Ernström, U., Sandberg, G. 1974. Stimulation of lymphocyte release from the spleen by theophylline and isoproterenol. *Acta Physiol. Scand.* 90: 202–9
288. Payan, D. G., Goetzl, E. J. 1985. Modulation of lymphocyte function by sensory neuropeptides. *J. Immunol.* 135: 783s–86s
289. Payan, D. G., Goetzl, E. J. 1987. Dual roles of substance P: modulator of immune and neuroendocrine functions. *Ann. NY Acad. Sci.* 512:465–75
290. Goetzl, E. J., Sreedharan, S. P., Harkonen, W. S. 1988. Pathogenetic roles of neuroimmunologic mediators. *Immunol. Allergy Clin. North Am.* 8:183–200
291. Hartung, H.-P., Wolters, K., Toyka, K. V. 1986. Substance P: Binding properties and studies on cellular responses in guinea pig macrophages. *J. Immunol.* 136:3856–63
292. Hartung, H. P., Toyka, K. V. 1983. Activation of macrophages by substance P: induction of oxidative burst and thromboxane release. *Eur. J. Pharmacol.* 89:301–5
293. Ruff, M. R., Wahl, S. M., Pert, C. B. 1985. Substance P receptor-mediated chemotaxis of human monocytes. *Peptides* 6:107–11
294. Foreman, J. C., Jordan, C. C. 1983. Histamine release and vascular changes induced by neuropeptides. *Agents Actions* 13:105–11
295. Foreman, J. C., Jordan, C. C., Piotrowski, W. 1982. Interaction of neurotensin with the substance P receptor mediating histamine release from rat mast cells and the flare in human skin. *Br. J. Pharmacol.* 77:531–39
296. Payan, D. G., Brewster, D. R., Missirian-Bastian, A., Goetzl, E. J. 1984. Substance P recognition by a subset of

human T lymphocytes. *J. Clin. Invest.* 74:1532–39
297. Stanisz, A. M., Scicchitano, R., Dazin, P., Bienenstock, J., Payan, D. G. 1987. Distribution of substance P receptors on murine spleen and Peyer's patch T and B cells. *J. Immunol.* 139:749–54
298. Wiedermann, C. J., Sertl, K., Pert, C. B. 1986. Substance P receptors in rat spleen: Characterization and autoradiographic distribution. *Blood* 68: 1398–401
299. Stanisz, A. M., Befus, D., Bienenstock, J. 1986. Differential effects of vasoactive intestinal peptide, substance P, and somatostatin on immunoglobulin synthesis and proliferations by lymphocytes from Peyer's patches, mesenteric lymph nodes, and spleen. *J. Immunol.* 136: 152–56
300. Scicchitano, R., Bienenstock, J., Stanisz, A. M. 1988. In vivo immunomodulation by the neuropeptide substance P. *Immunology* 63:733–35
301. Goetzl, E. J., ed. 1985. Supplement on neuromodulation of immunity and hypersensitivity. *J. Immunol.* 135:7395–8625
302. Bhathena, S. J., Louie, J., Schechter, G. P., Redman, R. S., Wahl, L., Recant, L. 1981. Identification of human mononuclear leukocytes bearing receptors for somatostatin and glucagon. *Diabetes* 30:127–31
303. Stanisz, A. M., Scicchitano, R., Payan, D. G., Bienenstock, J. 1987. In vitro studies of immunoregulation of substance P and somatostatin. *Ann. NY Acad. Sci.* 496:217–25
304. O'Dorisio, M. S. 1988. Neuropeptide modulation of the immune response in gut associated lymphoid tissue. *Int. J. Neurosci.* 38:189–98
305. Fink, T., Weihe, E. 1988. Multiple neuropeptides in nerves supplying mammalian lymph nodes: messenger candidates for sensory and autonomic neuroimmunomodulation? *Neurosci. Lett.* 90:39–44
306. Blalock, J. E., Bost, K. L., Smith, E. M. 1985. Neuroendocrine peptide hormones and their receptors in the immune system. Production, processing and action. *J. Neuroimmunol.* 10:31–40
307. Blalock, J. E. 1989. A molecular basis for bidirectional communication between the immune and neuroendocrine system. *Physiol. Rev.* 69:1–32
308. Makinodan, T., Adler, W. H. 1975. Effects of aging on the differentiation and proliferation potentials of the immune system. *Fed. Proc.* 34:153–58
309. Smith, E. M., Harbour-McMenamin, D., Blalock, J. E. 1985. Lymphocyte production of endorphins and endorphin-mediated immunoregulatory activity. *J. Immunol.* 135:779s–782s
310. Smith, E. M., Phan, M., Kruger, T. E., Coppenhaver, D. H., Blalock, J. E. 1983. Human lymphocyte production of immunoreactive thyrotropin. *Proc. Natl. Acad. Sci. USA* 80:6010–13
311. Hall, N. R., McGillis, J. P., Spangelo, B. L., Goldstein, A. L. 1982. Evidence that thymosins and other biologic response modifiers can function as neuroactive immunotransmitters. *J. Immunol.* 135:806s–11s
312. Hall, N. R., McGillis, J. P., Spangelo, B. L., Henly, D. L., Chrousos, G. P., et al. 1985. Thymic hormone effects on the brain and neuroendocrine circuits. In *Neural Modulation of Immunity,* ed. R. Guillemin, M. Cohn, T. Melnechuk, pp. 179–96. New York: Raven
313. Beckner, S. K., Farrar, W. L. 1988. Potentiation of lymphokine-activated killer cells differentiation and lymphocyte proliferation by stimulation of protein kinase C or inhibition of adenylate cyclase. *J. Immunol.* 140:208–14
314. Dailey, M. O., Schreurs, J., Schulman, H. 1988. Hormone receptors on cloned T lymphocytes. Increased responsiveness to histamine, prostaglandins and β-adrenergic agents as a late stage event in T cell activation. *J. Immunol.* 140: 2931–36
315. Besedovsky, H. O., Da Prada, M., del Rey, A. E., Sorkin, E. 1981. Immunoregulation by sympathetic nervous system. *Trends Pharmacol. Sci.* 2:236–38
316. Besedovsky, H. O., del Rey, A., Sorkin, E., Da Prada, M., Keller, H. H. 1979. Immunoregulation mediated by the sympathetic nervous system. *Cell. Immunol.* 48:346–55
317. del Rey, A., Besedovsky, H. O., Sorkin, E., Da Prada, M., Arrenbrecht, S. 1981. Immunoregulation mediated by the sympathetic nervous system. *Cell. Immunol.* 63:329–34
318. Carlson, S. L., Felten, D. L., Livnat, S., Felten, S. Y. 1987. Alterations of monoamines in specific central autonomic nuclei following immunization in mice. *Brain Behav. Immun.* 1:52–63
319. Besedovsky, H., del Rey, A. E., Sorkin, E., Dinarello, C. A. 1986. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science* 233:652–54
320. Besedovsky, H. O., del Rey, A., Sor-

kin, E., Lotz, W., Schwulera, U. 1985. Lymphoid cells produce an immunoregulatory glucocorticoid increasing factor (GIF) acting through the pituitary gland. *Clin. Exp. Immunol.* 59:622–28

321. Dunn, A. J. 1988. Systemic interleukin-1 administration stimulates hypothalamic norepinephrine metabolism paralleling the increased plasma corticosterone. *Life Sci.* 43:429–35
322. Berecek, K. H., Brody, M. J. 1982. Evidence for a neurotransmitter role for epinephrine derived from the adrenal medulla. *Am. J. Physiol.* 242:H593–H601
323. Cohen, R. A. 1985. Platelet-induced neurogenic coronary contractions due to accumulation of the false neurotransmitter, 5-hydroxytryptamine. *J. Clin. Invest.* 75:286–92
324. Bouchon, R., Will, B. 1982. Effects of early enriched and restricted environments on the exploratory and locomotor activity of dwarf mice. *Behav. Neural Biol.* 35:174–86
325. Hotchin, J., Seegal, R. 1978. Alterations in behavior resulting from persistent lymphocytic choriomeningitis virus infection. *Birth Defects Orig. Artic. Ser.* 14:171–78
326. Root-Bernstein, R. S., Westfall, F. C. 1984. Serotonin binding sites: I. Structure sites on myelin basic protein, LHRH, MSH, ACTH, interferon, serum albumin, ovalbumin, and red pigment concentrating hormone. *Brain Res. Bull.* 12:425–36