Digestive Diseases and Sciences, Vol. 33 No. 3 (March 1988 Supplement), pp. 41S–49S

Neuroendocrine Modulation Of The Immune System

Possible Implications for Inflammatory Bowel Disease

FERGUS SHANAHAN, MD, and PETER ANTON, MD

Evidence for neuroendocrine regulation of the immune system is reviewed. This includes human clinical studies of the influence of psychological stress on immune function, direct experimentation in animals, including classical Pavlovian conditioning of the immune response, modulation of immune function in vitro *by chemical messengers such as neuropeptides, the finding of receptors for neuropeptides on immunocytes, and the demonstration that lymphoid tissue is directly innervated. Secretory products of the immune system, which include interleukins and neuropeptides, may also influence the neuroendocrine system. Communication between the two systems is therefore bidirectional. The potential importance of the neuropeptide-immunocyte interaction within the intestinal mucosal immune system is emphasized, and its possible relevance in inflammatory disorders is discussed. This aspect of the "gut-brain" interaction deserves further study.*

KEYWORDS: neuroendocrine; psychoneuroimmunology; neuropeptides; immune system; inflammatory bowel disease; lymphocyte; receptor.

The primary function of the immune system is to distinguish self from nonself and to facilitate the elimination of material which is foreign to the host. Malfunction of this homeostatic process creates the potential for self-destruction (autoimmune disease) and/or opportunistic tumors or infection. Therefore, a fundamental feature of the immune system is its exquisitely precise regulation. Immunoregulatory mechanisms operate on several levels. Those that have received most attention include: genetic influences, helper/suppressor and contrasuppressor circuits, idiotype–antiidiotype networks, antibody feedback, and regulatory factors (cytokines). However, such mechanisms are autoregulatory. Intuitively, it seems unlikely that the immune system differs from other homeostatic systems by operating entirely in an autonomous fashion within self-contained circuits and feedback loops. Rather, one might expect that it would be subject to additional and more integrative regulatory signals on a different level from the central nervous system.

The notion that immunological reactions and putative immunologically mediated diseases might be influenced by the nervous system is not new. However, recent studies have considerably advanced our understanding of the interaction between the immune sys-

From the Department of Medicine, UCLA School of Medicine, Los Angeles, California, and the Harbor/UCLA Inflammatory Bowel Disease Center.

Supported by the Harbor/UCLA Inflammatory Bowel Disease NIH Center grant AM 36200 and the Blinder Crohn's Disease Research Foundation. Dr. Shanahan is a recipient of a career development award from the National Foundation for Ileitis and Colitis.

Address for reprint requests: Dr. Fergus Shanahan, Department of Medicine, Division of Gastroenterology, UCLA School of Medicine, Center for the Health Sciences, 10833 Le Conte Avenue, Los Angeles, CA 90024.

0163-2116/88/0300-041S$06.00/0 © 1988 Plenum Publishing Corporation

tem and the nervous system. Evidence for a reciprocal or bidirectional communication between the two systems is rapidly emerging. This should influence our approach to the study of the intestinal mucosal immune system and may have particular relevance to inflammatory bowel disease.

Our purpose here is to summarize briefly and overview the evidence for neuroimmunological interactions and to highlight certain concepts of potential significance for mucosal immunopathology. The references are intended to be representative, not comprehensive, and include several excellent reviews that may be consulted for an extended list of references on specific aspects of this field.

EVIDENCE FOR NEUROIMMUNOREGULATION

The evidence for neuroimmunomodulation has been unfolding on several levels. These include: (1) clinical studies in which some form of psychological stress is correlated with alterations in immunological function; (2) direct experimental evidence from animal studies such as the effects of graded stress, specific brain lesions, and classical Pavlovian conditioning on the immune system; (3) the analysis of immunocyte function *in vitro* under the influence of chemical messengers which have traditionally been considered to be neurotransmitters or neuroendocrine peptides; (4) the finding of surface receptors for neuropeptides; and (5) the demonstration that lymphoid tissue is directly innervated.

Human Clinical Studies. Clinicians have long suspected that psychological factors may influence the course of several diseases including those which are thought to be immunologically mediated. The medical literature is sprinkled with interesting reports and fascinating observations on the role of psychosomatic phenomena and the influence of stress on immunocompetence and disease susceptibility (1–4). Examples include the inhibition of the delayed hypersensitivity response to tuberculin in the Mantoux test by direct suggestion under hypnosis (5) and the delayed recovery from influenza in depressed patients compared with controls (6).

Several recent, carefully controlled, prospective studies have demonstrated that a variety of stressful circumstances, including bereavement (7, 8), depression (9–11), marital disruption (10), and the preexamination torment experienced by medical students (12, 13), are associated with significant alterations in immune function. Such studies, although exciting, should be interpreted with caution (11, 14). They do not prove a direct causal link between stress and the observed immunological alteration. Compounding factors such as alterations in diet, drug therapy, and disturbed sleep patterns might influence the results (14). In addition, the immunological parameters studied have generally been crude assessments of immunocompetence (lymphocyte enumeration, lymphocyte blastogenesis, natural killer activity, and nonspecific immunoglobulin levels), have wide ranges of normality, and are of uncertain significance in regards to disease susceptibility.

Animal Studies—Direct Experimentation. Animal studies have been helpful in measuring the influence of stress on the immune response. As early as 1878, Pasteur observed an increased susceptibility to anthrax in chickens stressed by cold water immersion (15). Controlled experiments using graded, stressful stimuli indicate that immune suppression or enhancement may occur, depending on the nature and strength of the stimulus and the duration of exposure. In these experiments, increasing intensity of electrical shock was proportional to the consequent immunosuppression (16), and short-term exposure to noise was suppressive, whereas chronic exposure resulted in immunoenhancement (17). The mechanisms of stress-induced immune alteration are multiple and complex (9, 18) and are not solely related to the hypothalamic–pituitary–adrenal axis, as evidenced by control experiments with adrenalectomized animals (19).

That classical Pavlovian behavioral conditioning may modify the immune response was extensively illustrated by multiple investigators in the Russian literature (4). In the same way as Pavlov showed that gastrointestinal and salivary secretions could be behaviorally conditioned, other investigators, over 50 years ago, began to apply the same approach to the immune system. In a typical experiment, guinea pigs would receive repeated peritoneal injections of bacterial filtrate, each of which would stimulate an immune response with peritoneal exudation. Each injection would be paired with an unrelated stimulus such as skin scratching. After a rest period, scratching alone produced similar peritoneal exudates (4). More recently, Ader (4) and Ader and Cohen (20) have clearly shown that behavioral conditioning programs can be used to achieve humoral and cellular immunosuppression. The magnitude of the conditioning effect, although not large, is consistent, and others have confirmed these results (21, 22). In addition to immunosup-

pression, behavioral conditioning can also be used to bring about enhancement of immune reactivity (23). Thus, animals can "learn" to suppress or enhance their immune response. The potential clinical importance of these experiments is underlined by the demonstration that immunosuppression produced by conditioning can modify the course of autoimmune disease, as in murine lupus (24).

A more direct approach to the study of the neuroendocrine–immunocyte axis has been the examination of immunological function in animals with chemical or electrolytic lesions in specific areas of the brain such as the anterior hypothalamus and limbic nuclei (25–28). Suppression or enhancement of certain immunological parameters may be observed depending on the site of the lesion (27).

MEDIATORS OF NEUROIMMUNOMODULATION

The mechanism by which the neuroendocrine system communicates with the immune system is the same as with the other systems: delivery of chemical messengers to end-organ receptors. The route by which these mediators reach their target cell (neurocrine, paracrine, or endocrine) varies depending on the mediator, the immune effector cell, and the tissue location of that cell. Although circulating leukocytes have been used in most human studies because of their accessibility, these cells are probably best suited for studies of endocrine-mediated immunomodulation. Neurocrine control may be more important within certain tissues and lymphoid structures. The anatomic basis for this is the convincing demonstration of peptidergic and noradrenergic innervation of mast cells and lymphoid tissues, including the mucosal associated tissue (29, 30). These nerve terminals are associated with lymphocytes and are not simply influencing the vasculature of lymphoid tissue. In addition, APUD (amine precursor uptake and decarboxylation) cells within lymphoid tissue (31) may exert a paracrine influence.

A large variety of mediators has been implicated in the immunomodulatory effects of the neuroendocrine system. The broad-spectrum effects of steroid hormones and catecholamines on the immune system are well known (32-37) and alterations in the levels of these agents have been reported in stress and depression (34, 37, 38). However, the focus of recent research has been on the growing list of peptides that may have more specific effects on immune function. Table 1 is a representative list of peptides which have been shown to influence various immune effector cells *in vitro*. A multitude of effects have been observed and include alterations in immunoglobulin production, lymphocyte mitogenesis, nonspecific cytotoxicity, mast cell–basophil secretion, chemotaxis,

TABLE 1. FUNCTIONAL EFFECTS OF NEUROPEPTIDES ON IMMUNOCYTES

Mediator	*Immune cell*	*Effects*	*Reference*
Substance P	T cell	enhanced proliferation	39
	B cell	enhanced IgA production	40
	monocyte	increased chemotaxis	41
	neutrophil	lysozyme release	42
	neutrophil	increased phagocytosis	43
	mast cell	secretion	44, 45
VIP	T cell	inhibition of proliferation	46
	T cell	altered migration	47
	T cell	increased cyclic AMP	48
	NK cell	increased cytotoxicity	49
	B cell	increased IgM, decreased IgA	40
	mast cell	secretion	44, 45
Somatostatin	lymphocyte	decreased proliferation	40
	lymphocyte	decreased IgA	40
	mast cell	secretion	44, 45
	basophil	inhibition of release	50
β-Endorphin	T cell	altered mitogenesis	51, 52
	NK cell	increased cytotoxicity	53
	mast cell	secretion	44, 45
Enkephalin	B cell	decreased Ig	54
	NK cell	increased cytotoxicity	53
ACTH	B cell	decreased Ig	54
Growth hormone	T cell	induces cytotoxicity	55

phagocytosis, neutrophil lysosomal release, and lymphocyte homing. In certain instances, there is evidence from radiolabeled peptide binding studies which suggests that these effects are receptor mediated (Table 2). In some cases these receptors appear to be similar, if not identical, to those found in the neuroendocrine system (59).

TISSUE-DEPENDENT DIFFERENCES IN THE NEUROPEPTIDE–IMMUNE AXIS

Neuroendocrine immune regulation is likely to have its greatest biological significance in the intestine and within other mucosal tissues. Many of the *in vitro* functional studies were performed using circulating leukocytes; immunocytes resident within mucosal tissues, which are exposed to relatively high concentrations of neuropeptides (64, 65) and possibly functionally active dietary peptides (66), may exhibit different patterns of responsiveness.

The mucosal and systemic immune systems, although complementary with respect to host defense, are largely independent of each other. Mucosal effector cells have been shown repeatedly to differ functionally and phenotypically from their counterparts within the systemic immune system (67). Therefore, differences in neuroendocrine regulation would not be surprising. In the rat, a wide variety of neuropeptides including somatostatin, substance P, VIP, neurotensin, and endorphins are known to induce mast cell secretion at nonmucosal sites, but only substance P has secretagogue effects on mucosal mast cells (44, 68). In addition, there is indirect evidence that somatostatin may be inhibitory to mucosal mast cells (69).

Another example of the differential effect of neuropeptides on mucosal and systemic immune events is the recent demonstration that the effects of VIP, somatostatin, and substance P on immunoglobulin production *in vitro* are not only isotype- and peptide-specific but also tissue-specific (40). The most pronounced effects are noted in the mucosal associated lymphoid tissues.

Neuropeptides may also influence the migration and homing patterns of immune effector cells (70). This is directly relevant to mucosal immune cell traffic. Elegant studies by Ottaway (47) have shown that VIP alters the migration of T cells through mucosal associated lymphoid tissue. Preincubation of radiolabeled mouse T cells *in vitro* with VIP resulted in a dose-dependent reduction in their subsequent *in vivo* localization within Peyer's patches and mesenteric lymph nodes but not within the spleen and other major organs.

INFLUENCE OF IMMUNE SYSTEM ON NEUROENDOCRINE SYSTEM

It has become clear in recent years that communication between the neuroendocrine system and the immune system is bidirectional (Figure 1). Thus, the immune system not only receives regulatory signals from the central nervous system, but it also appears to be capable of providing information to the central nervous system. Three lines of evidence support this concept. First, immune responses in rats have been associated with increased neural firing detected by electrodes implanted in the medial hypothalamus (71, 72). Immune challenge in these animals elicited a reduction in the synthesis and content of noradrenaline within the hypothala-

TABLE 2. NEUROPEPTIDE RECEPTORS ON IMMUNE CELLS

Mediator	*Immune cell*	*Dissociation constant*	*Reference*
Substance P	T cell	0.18 μM	56
	lymphoblast (IM-9)	0.65 nM	57
	monocyte	20 nM	58
VIP	T cell	5 nM	46
	T cell	0.47 nM	59
	lymphoblast (Molt 4)	7 nM	59
	monocyte	0.25 nM, 25 nM	60
Neurotensin	macrophage	0.9 nM, 28 nM	61
Somatostatin	lymphocyte	0.5 μM	62
	monocyte	0.5 μM	62
β-Endorphin	lymphocyte	0.5 nM	51
Enkephalin	lymphocyte	0.59 nM	54
ACTH	lymphocyte	0.1 nM, 4.8 nM	54
Growth hormone	lymphocyte	1.3 nM	63

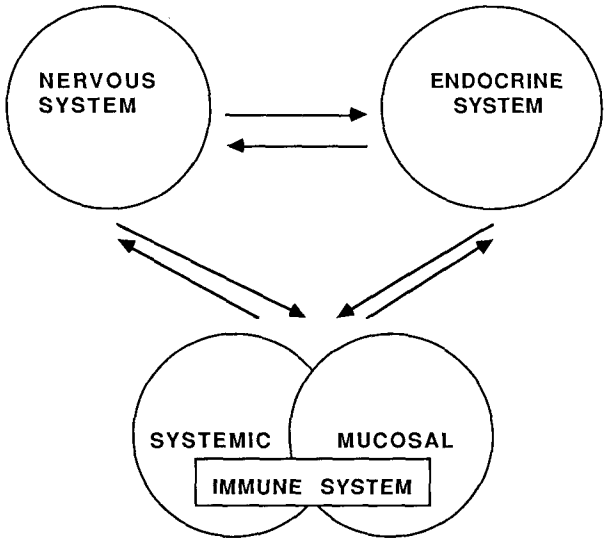

Fig 1. Intercommunication between the neuroendocrine system and the immune system.

mus. This effect can be mimicked by injection of supernatants from immunological cells which have been activated *in vitro* (72). Second, secretory products of the immune system, traditionally considered to be lymphokines including interleukins and interferons, have been shown to influence the nervous system (73, 74). Parenthetically, these and other chemical mediators of the immune system should no longer be considered to be exclusively produced by immunocytes; interleukin 1 for example, is produced by several nonlymphoid cells including astrocytes (75). Third, mediators, which classically have been thought to be synthesized solely by neuroendocrine tissues, are known to be produced by immunocytes (Table 3). This might at first seem unexpected, but the same or very similar molecules also occur in primitive unicellular organisms (83, 84) where they appear to mediate intercellular communication. Intercellular peptide messengers probably occurred very early in evolution and are remarkably well conserved (83, 84). That the immune system might employ these same messengers should not be surprising.

Our understanding of intercellular communication and regulatory molecules is continually being revised and broadened. It is becoming increasingly evident that rigorous distinctions between lymphokines, growth factors, cytokines, local hormones, neuropeptides, and neurotransmitters are no longer appropriate (85, 86). For example, a novel growth factor that is both a lymphokine product of lectin-activated T cells with B cell modulatory effects and also a neurotrophic factor for spinal and sensory neurons has recently been described (87, 88).

The weight of evidence indicates that neuropeptide-like molecules produced by lymphocytes have the same biological effects as those produced by the neuroendocrine system and share antigenic and chemical features (86). The type of peptide produced by activated lymphocytes depends on the nature of the stimulus (virus, bacterium, or chemical): Newcastle virus infection of lymphocytes results in ACTH secretion, whereas stimulation by staphylococcal enterotoxin A leads to TSH production (81). This differential mediator release implies that the immune system can sense differences between environmental stimuli and adjust its secretory response accordingly. Since the mediators that are released are themselves neuroendocrine substances, they provide the central nervous system with ongoing feedback information. Blalock (89) has therefore likened the immune system to a sensory organ that responds to environmental stimuli—infectious and neoplastic—which are not recognized by classical sensory modalities.

IMPLICATIONS FOR CHRONIC INFLAMMATORY DISORDERS

Immunological effector mechanisms have a prominent role in mediating the tissue damage in inflammatory bowel disease (90, 91). Psychosomatic factors such as stress probably never initiate inflammation, but there is a widely held clinical suspicion that they may influence the subsequent course and disease activity in some patients. The link between stress and the inflammatory process may be through the neuroendocrine–immune axis. Even if the trigger factor proves to be an infectious agent, the host's immune system is likely to be an important contributor to disease pathogenesis and chronicity, either because of a failure to clear the infectious agent and/or because of its inappropriate response to that agent. Specific regulatory abnormalities of the mucosal immune system are therefore being pursued by several investigators. Neuroendocrine–immune interactions may prove to be a fundamental component of these abnormalities and offer a new and exciting approach to these diseases.

Disease activity would be influenced by alterations in the tissue levels of neuropeptides or in the sensitivity of immune effector cells to these pep-

TABLE 3. NEUROENDOCRINE PEPTIDES PRODUCED BY IMMUNE CELLS

Peptide	*Cell*	*Reference*
VIP	neutrophil, mast cell	76, 77
Somatostatin	rat basophil leukemia line	78
β-Endorphin	lymphocyte, monocyte, macrophage	79, 80
ACTH	lymphocyte, macrophage	79, 80
TSH	lymphocyte	81
Growth hormone	lymphocyte	82
FSH/LH	lymphocyte	82
Chorionic gonadotropin	lymphocyte	82

tides. Recent evidence for a direct involvement of substance P in mediating tissue injury in experimental and rheumatoid arthritis may have implications for the pathogenesis or perpetuation of inflammatory bowel disease (92, 93). The peptide concentration of nerve terminals innervating inflamed joints is increased (94), and the severity of the arthritis has been shown to be, at least in part, attributable to the actions of substance P (92). Similarly, in ulcerative colitis an increase in mucosal adrenergic nerves and enterochromaffin cells has been reported (95); in Crohn's disease there is an increase in ganglion cells (96, 97) and in the content of VIP and number of VIP-containing nerves in the intestinal wall (98). Although these changes may be secondary phenomena (99), they could have significant effects *in vivo* on specific aspects of mucosal lymphocyte function, including traffic and migration patterns (47).

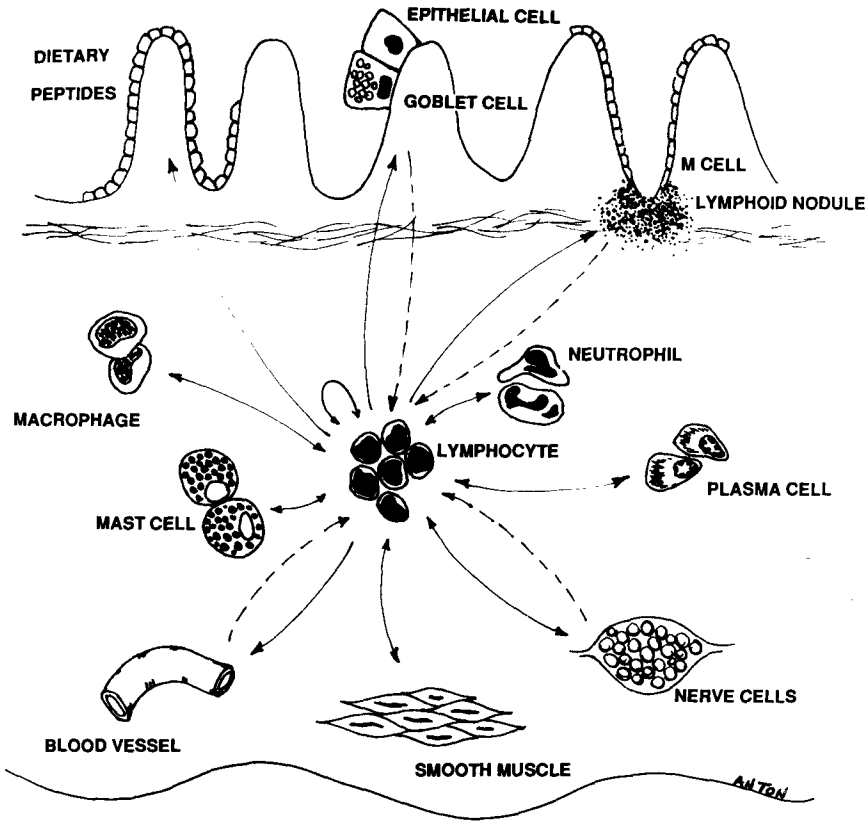

Fig 2. Schematic representation of intercommunications between immune cells and gut wall structures including effects on other immunocytes, vascularity, motility, and epithelial cell function. Mediators include neuropeptides, hormones, lymphokines, arachidonate metabolites, and vasoactive amines.

However, to date, studies of human mucosal lymphocyte function in inflammatory bowel disease have been limited to nonspecific assays such as cytotoxicity, blastogenesis, and immunoglobulin secretion, frequently with unfractionated cell preparations (90, 91).

Altered sensitivity or inappropriate responses by immune effector cells to the regulatory effects of neuropeptides is probably more important than variations in tissue peptide concentration. Preliminary results from this laboratory indicate that the responsiveness of neutrophils from patients with familial Mediterranean fever to substance P and to the synthetic bacterial peptide f-Met-Leu-Phe is significantly enhanced over control values (100). Whether this is a primary abnormality or secondary to the disease process is not yet clear. Similar studies of peptide–immunocyte interaction in inflammatory bowel disease will require meticulous isolation and enrichment of specific mucosal effector cell subsets.

Finally, the potential relevance of neuropeptide–immune interactions becomes intriguing when one considers that cellular components of the mucosal inflammatory process may themselves elaborate potent neuropeptide mediators including VIP (Table 3). In addition to the autocrine effects of these endogenously produced peptides on the mucosal immune system, they may exert a paracrine influence on epithelial and goblet cell secretion, smooth muscle activity, and vascular permeability (Figure 2). Thus, the local mucosal immune system in concert with the nervous system may orchestrate a complicated web of intercommunicating chemical messenger systems far greater than previously considered (101–103).

REFERENCES

1. Solomon GF, Amkraut AA: Psychoneuroendocrinological effects on the immune response. Annu Rev Microbiol 35:155–184, 1981
2. Tecoma ES, Huey LY: Psychic distress and the immune response. Life Sci 36:1799–1812, 1985
3. Locke S, Ader R, Besedovsky Hall N, Solomon G, Strom T, Spector NH (eds): Foundations of Psychoneuroimmunology. New York, Aldine Publishing, 1985
4. Ader R: Psychoneuroimmunology. London, Academic Press, 1981
5. Black S, Humphrey JH, Niven JSF: Inhibition of mantoux reaction by direct suggestion under hypnosis. Br Med J 6:1649–1952, 1965
6. Imboden JB, Canter A, Cluff LE: Convalescence from influenza. A study of the psychological and clinical determinants. Arch Intern Med 108:393–399, 1961
7. Bartrop RW, Lazerus L, Luckhurst E, Kiloh LG, Penny R: Depressed lymphocyte function after bereavement. Lancet 1:834–836, 1977
8. Schleifer SJ, Keller SE, Camerino E, Thomton JC, Stein M: Suppression of lymphocyte stimulation following bereavement. JAMA 250:374–378, 1983
9. Stein M, Keller SE, Schleifer SJ: Stress and immunomodulation: The role of depression and neuroendocrine function. J Immunol 135:827s–833s, 1985
10. Kiecolt-Glaser JK, Glaser R: Psychological influences on immunity. Psychosomatics 27:621–624, 1986
11. Denman AM: Immunity and depression. Br Med J 293: 464–465, 1986
12. Kiecolt-Glaser JK, Glaser R, Strain JC, Stout JC, Tarr KL, Holliday JE, Speicher CE: Modulation of cellular immunity in medical students. J Behav Med 9:5–21, 1986
13. Kiecolt-Glaser JK, Glaser R, Stout JC, Tarr KL, Speicher CE, Holliday JE: Stress-related impairments in cellular immunity. Psychiatry Res 16:233-239, 1985
14. Cohen JJ: Immunity and behavior. J Allergy Clin Immunol 79:2–5, 1987
15. Pasteur L, Joubert J, Chamberland: Le charbon des poules. Compt Rend Acad Sci 87:47–48, 1878
16. Keller SE, Weiss JM, Schleifer SJ, Miller NE, Stein M: Suppression of immunity by stress: Effect of a graded series of stressors on lymphocyte stimulation in the rat. Science 213:1397–1399, 1981
17. Monjan AA, Collector MI: Stress-induced modulation of the immune response. Science 196:307–308, 1977
18. Shavit Y, Lewis JW, Terman GW, Gale RP, Liebeskind JC: Opioid peptides mediate the suppressive effect of stress on natural killer cell cytotoxicity. Science 223:188–190, 1984
19. Keller SE, Weiss JM, Schleifer SJ, Miller NE, Stein M: Stress induced immunosupression of immunity in adrenalectomized rats. Science 221:1301–1304, 1983
20. Ader R, Cohen N, Bovjerg D: Immunoregulation by behavioral conditioning. Trends Pharmacol Sci 4: 78–80, 1983
21. Rodgers MP, Reich P, Strom TB, Carpenter CB: Behaviorally conditioned immunosuppression: Replication of a recent study. Psychosomat Med 38:447–451, 1976
22. Wayner EA, Flannery GR, Singer G: Effects of taste aversion conditioning on the primary antibody response to sheep red blood cells and *Brucella abortus* in the albino rat. Physiol Behav 21:995–1000, 1978
23. Russell M, Dark KA, Cummins RW, Ellman G, Callaway E, Peeke HVS: Learned histamine release. Science 225:733-734, 1984
24. Ader R, Cohen N: Behaviorally conditioned immunosuppression and murine systemic lupus erythematous. Science 215:1534–1536, 1982
25. Korneva EA, Khai LM: Effect of destruction of the hypothalamic areas on immunogenesis. Fiziol Zh SSSR 49:T88–T92, 1963
26. Jankovic BD, Isakovic K: Neuro-endocrine correlates of immune response. I. Effects of brain lesions on antibody production, arthus reactivity, and delayed hypersensitivity in the rat. Int Arch Allergy 45:360–372, 1973
27. Brooks WH, Cross RJ, Roszman TL, Markesbery WR: Neuroimmunomodulation: Neural anatomical basis for impairment and facilitation. Ann Neurol 12:56–61, 1982
28. Roszman TL, Brooks WH: Neural modulation of immune function. J Neuroimmunol 10:59–69, 1985

29. Felten DL, Felten SY, Carlson SL, Olschowka JA, Livnat S: Noradrenergic and peptidergic innervation of lymphoid. J Immunol 135:755s–765s, 1985
30. Newson B, Dahlstrom A, Enerback L, Ahlman H: Suggestive evidence for a direct innervation of mucosal mast cells. Neuroscience 10:565, 1983
31. Angeletti RH, Hickey WF: A neuroendocrine marker in tissues of the immune system. Science 230:89–90, 1985
32. Stevenson HC, Fauci AS: Effects of corticosteroids on the function and distribution of human lymphocytes. *In* Clinical Immunology Update. EC Franklin (ed). New York, Elsevier, 1981, pp 337–355
33. Comsa J, Leonhardt H, Wekerle H: Hormonal coordination of the immune response. Rev Physiol Biochem Pharmacol 92:115–191, 1982
34. Axelrod J, Reisine TD: Stress hormones: Their interaction and regulation. Science 224:452–459, 1984
35. Ahmed SA, Penhale WJ, Talal N: Sex hormones, immune responses and autoimune diseases. Mechanism of sex hormone action. Am J Pathol 121:531–551, 1985
36. Schleimer RP: The mechanisms of antiinflammatory steroid action in allergic diseases. Annu Rev Pharmacol Toxicol 25:381–412, 1985
37. Mann JJ, Brown RP, Halper JP, Sweeney JA, Kocsis JH, Stokes PE, Bilezikian JP: Reduced sensitivity of lymphocyte beta-adrenergic receptors in patients with endogenous depression and psychomotor agitation. N Engl J Med 313: 715–720, 1985
38. Riley V: Psychoneuroendocrine influences on immunocompetence and neoplasia. Science 212:1100–1109, 1981
39. Payan DG, Brewster DR, Goetzl EJ: Specific stimulation of human T lymphocytes by substance P. J Immunol 131:1613–1615, 1983
40. Stanisz AM, Befus D, Bienenstock J: Differential effects of vasoactive intestinal polypeptide, substance P, and somatostatin on immunoglobulin synthesis and proliferations by lymphocytes from Peyer's Patches, mesenteric lymph nodes, and spleen. J Immunol 136:152–156, 1986
41. Ruff MR, Wahl SM, Pert CB: Substance P receptor-mediated chemotaxis of human monocytes. Peptides 6(suppl 2):107–111, 1985
42. Marasco WA, Showell HJ, Becker EL: Substance P binds to the formylpeptide chemotaxis receptor on the rabbit neutrophil. Biochem Biophys Res Commun 99:1065–1072, 1981
43. Bar-Shavit Z, Goldman R, Stabinsky Y, Gottlieb P, Fridkin M, Teichberg VI, Blumberg S: Enhancement of phagocytosis—a newly found activity of substance P residing in its *N*-terminal tetrapeptide sequence. Biochem Biophys Res Commun 94:1445–1450, 1980
44. Shanahan F, Denburg JA, Fox J, Bienenstock J, Befus D: Mast cell heterogeneity: Effect of neuroenteric peptides on histamine release. J Immunol 135:1331–1337, 1985
45. Foreman JC, Piotrowski W: Peptides and histamine release. J Allergy Clin Immunol 74:127–131, 1984
46. Ottaway CA, Greenberg GR: Interaction of VIP with mouse lymphocytes: Specific binding and the modulation of mitogen responses. J Immunol 132:417–423, 1984
47. Ottaway CA: *In vitro* alteration of receptors for vasoactive intestinal peptide changes the *in vivo* localization of mouse T cells. J Exp Med 160:1054–1069, 1984
48. O'Dorisio MS, Hermina NS, O'Dorisio TM, Balcerzak SP: Vasoactive intestinal polypeptide modulation of lymphocyte adenylate cyclase. J Immunol 127:2551–2554, 1981
49. Rola-Pleszcynski M, Bolduc D, St-Pierre S: The effects of VIP on human natural killer cells. J Immunol 135:2569–2573, 1985
50. Goetzl EJ, Payan DG: Inhibition by somatostatin of the release of mediators from human basophils and rat leukemic basophils. J Immunol 133:3255–3259, 1984
51. Gilman SC, Schwartz JM, Milner RJ, Bloom FE, Feldman JD: β-Endorphin enhances lymphocyte proliferative responses. Proc Natl Acad Sci USA 79:4226–4230, 1982
52. McCain HW, Lamster IB, Buzzone JM, Grbic JT: β-Endorphin modulates human immune activity via non-opiate receptor mechanisms. Life Sci 31:1619–1624, 1982
53. Mathews PM, Froelich CJ, Sibbit WL, Bankhurst AD: Enhancement of natural cytotoxicity by β-endorphin. J Immunol 130:1658–1662, 1983
54. Johnson HM, Smith EM, Torres BA, Blalock JE: Regulation of the *in vitro* antibody response by neuroendocrine hormones. Proc Natl Acad Sci USA 79:4171–4173, 1982
55. Snow EC, Feldbush TL, Oaks JA: The effect of growth hormone and insulin upon MLC responses and the generation of cytotoxic lymphocytes. J Immunol 126:161–164, 1981
56. Payan DG, Brewster DR, Missirian-Bastien A, Goetzl EJ: Substance P recognition by a subset of human T lymphocytes. J Clin Invest 74:1532–1539, 1984
57. Payan DG, McGillis JP, Organist ML: Characterization of the lymphocyte substance P receptor. J Biol Chem 261:14321–14329, 1986
58. Hartung H-P, Wolters K, Toyka KV: Substance P: Binding properties and studies on cellular responses in guinea pig macrophages. J Immunol 136:3856–3863, 1986
59. O'Dorisio MS: Biochemical characteristics of receptors for vasoactive intestinal polypeptide in nervous, endocrine, and immune systems. Fed Proc 46:192–195, 1987
60. Wiik P, Opstad PK, Boyum A: Binding of vasoactive intestinal polypeptide (VIP) by human blood monocytes: Demonstration of specific binding sites. Regul Peptides 12:145–153, 1985
61. Bar-Shavit Z, Terry S, Blumberg S, Goldman R: Neurotensin–macrophage interaction: Specific binding and augmentation of phagocytosis. Neuropeptides 2:325–335, 1982
62. Bhathena SJ, Louie J, Schechter GP, Redman RS, Wahl L, Recant L: Identification of human mononuclear leukocytes bearing receptors for somatostatin and glucagon. Diabetes 30:127–131, 1981
63. Lesniak MA, Gorden P, Roth J, Gavin JR: Binding of ^{125}I-human growth hormone to specific receptors in human cultured lymphocytes. J Biol Chem 249:1661–1667, 1974
64. Pearse AGE, Polak JM, Bloom SR: The newer gut hormones. Cellular sources, physiology, pathology, and clinical aspects. Gastroenterology 72:746–761, 1977
65. Gaginella TS, Mekhjian HS, O'Dorisio TM: Vasoactive intestinal peptide: Quantification by radioimmunoassay in isolated cells, mucosa, and muscle of the hamster intestine. Gastroenterology 74:718–721, 1978
66. Morley JE: Food peptides. A new class of hormones? JAMA 247:2379–2380, 1982
67. Bienenstock J, Befus AD: Mucosal immunology. Immunology 41:249–270, 1980
68. Shanahan F, Lee TDG, Bienenstock J, Befus AD: The

influence of endorphins on peritoneal and mucosal mast cell secretion. J Allergy Clin Immunol 74:499–504, 1984
69. Goetzl EJ, Chernov-Rogan T, Furuichi K, Goetzl LM, Lee JY, Renold F: Neuromodulation of mast cell and basophil function. *In* Mast Cell Differentiation and Heterogeneity. AD Befus, J Bienenstock, JA Denburg (eds). New York, Raven Press, 1986, pp 223–229
70. Moore TC: Modification of lymphocyte traffic by vasoactive neurotransmitter substances. Immunology 52:511–518, 1984
71. Besedovsky HO, Sorkin E, Felix D, Haas H: Hypothalamic changes during the immune response. Eur J Immunol 7:323–325, 1977
72. Besedovsky H, Del Rey A, Sorkin E, Da Prada M, Burri R, Honegger C: The immune response evokes changes in brain noradrenergic neurons. Science 221:564–566, 1983
73. Dinarello CA: Interleukin-1 and the pathogenesis of the acute-phase response. N Engl J Med 311:1413–1418, 1984
74. Hall NR, McGillis JP, Spangelo BL, Goldstein AL: Evidence that thymosins and other biologic response modifiers can function as neuroactive immunotransmitters. J Immunol 135:806s–811s, 1985
75. Fontana A, Weber E, Dayer J-M: Synthesis of interleukin 1/endogenous pyrogen in the brain of endotoxin-treated mice: A step in fever induction? J Immunol 133:1696–1698, 1984
76. O'Dorisio MS, O'Dorisio TM, Cataland S, Balcerzak SP: VIP as a biochemical marker for polymorphonuclear leukocytes. J Lab Clin Med 96:666–672, 1980
77. Cutz E, Chan W, Track N, Goth A, Said S: Release of vasoactive intestinal polypeptide in mast cells by histamine liberators. Nature 275:661–662, 1978
78. Goetzl EJ, Chernov-Rogan T, Cooke MP, Renold F, Payan DG: Endogenous somatostatin-like peptides of rat basophilic leukemia cells. J Immunol 135:2707–2712, 1985
79. Smith EM, Blalock JE: Human lymphocyte production of corticotropin and endorphin-like substances: Association with leukocyte interferon. Proc Natl Acad Sci USA 78:7530–7534, 1981
80. Lolait SJ, Lim ATW, Toh BH, Funder JW: Immunoreactive β-endorphin in a subpopulation of mouse spleen macrophages. J Clin Invest 73:277–280, 1984
81. Smith EM, Phan M, Kruger TE, Coppenhaver DH, Blalock JE: Human lymphocyte production of immunoreactive thyrotropin. Proc Natl Acad Sci USA 80:6010–6013, 1983
82. Blalock JE, Bost KL, Smith EM: Neuroendocrine peptide hormones and their receptors in the immune system. J Neuroimmunol 10:31–40, 1985
83. Roth J, LeRoith D, Shiloach J, Rosenzweig JL, Lesniak MA, Havrankova J: The evolutionary origins of hormones, neurotransmitters, and other extracellular chemical messengers. Implications for mammalian biology. N Engl J Med 306:523–527, 1982
84. LeRoith D, Shiloach J, Berelowithz M, Frohman LA, Liotta AS, Krieger DT, Roth J: Are messenger molecules in microbes the ancestors of the vertebrate hormones and tissue factors? Fed Proc 42:2602–2607, 1983
85. Schmitt FO: Molecular regulators of brain function: a new view. Neuroscience 13:991–1001, 1984
86. Blalock JE: Relationships between neuroendocrine hormones and lymphokines. Lymphokines 9:1–13, 1984
87. Gurney ME, Heinrich SP, Lee MR, Yin H-S: Molecular cloning and expression of neuroleukin, a neurotrophic factor for spinal and sensory neurons. Science 234:566–574, 1986
88. Gurney ME, Apatoff BR, Spear GT, Baumel MJ, Antel JP, Brown Bania M, Reder AT: Neuroleukin: A lymphokine product of lectin-stimulated T cells. Science 234:574–581, 1986
89. Blalock JE: The immune system as a sensory organ. J Immunol 132:1067–1070, 1984
90. Strober W, James SP: The immunologic basis of inflammatory bowel disease. J Clin Immunol 6:415–432, 1986
91. Shanahan F: Inflammatory bowel disease. *In* Immunology of Intestinal Disease. SR Targan (moderator). Ann Intern Med 106:862–866, 1987
92. Levine JD, Clark R, Devor M, Helms C, Moskowitz MA, Basbaum AL: Interneuronal substance P contributes to the severity of experimental arthritis. Science 226:547–549, 1984
93. Levine JD, Moskowitz MA, Basbaum AL: The contribution of neurogenic inflammation in experimental arthritis. J Immunol 135:843s–847s, 1985
94. Lembeck F, Donnerer J, Colpaert FC: Increase in substance P in primary afferent nerves during chronic pain. Neuropeptides 1:175–180, 1981
95. Kyosola K, Penttila O, Salaspuro M: Rectal mucosal adrenergic innervation and enterochromaffin cells in ulcerative colitis and irritable colon. Scand J Gastroenterol 12:363–367, 1977
96. Morson BC, Dawson IMP: Inflammatory disorders. *In* Gastrointestinal Pathology. BC Morson, IMP Dawson (eds). Oxford, Blackwell Scientific, 1972, pp 243–298
97. Davis DR, Dockerty MB, Mayo CW: The myenteric plexus in regional enteritis; a study of 24 cases. Surg Gynecol Obstet 101:208, 1955
98. Bishop AE, Polak JM, Bryant MG, Bloom SR, Hamilton S: Abnormalities of vasoactive intestinal polypeptide-containing nerves in Crohn's disease. Gastroenterology 79:853–860, 1980
99. Dawson J, Bryant MG, Bloom SR, Peters TJ: Gastrointestinal regulatory peptide storage granule abnormalities in jejunal mucosal diseases. Gut 25:636–643, 1984
100. Anton P, Durham M, Schwabe A, Targan S, Shanahan F: Enhanced sensitivity of neutrophils to f-Met-Leu-Phe in familial Mediterannean fever. J Clin Immunol 1988 (in press)
101. Castro GA: Immunological regulation of epithelial function. Am J Physiol 243:(Gastrointest Liver Physiol 6):G321–G329, 1982
102. Payan DG, McGillis JP, Goetzl EJ: Neuroimmunology. Adv Immunol 39:299–323, 1986
103. O'Dorisio MS: Neuropeptides and gastrointestinal immunity. Am J Med 81(suppl 6B):74–82, 1986