

III. Therapeutic and clinical implications of systemic allergic inflammation

Stress, chronic inflammation, and emotional and physical well-being: Concurrent effects and chronic sequelae

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The importance of T_H cells (specifically T_H2 cells) that produce IL-4, -5, -10, and -13 in the propagation of chronic allergic inflammation is well known. However, the role of the hypothalamic-pituitary-adrenal axis and the sympathetic system as immunomodulators of events leading to inflammation is less well established. Increases in stress levels are associated with elevations in circulating glucocorticoids and catecholamines, which may influence disease pathophysiologic factors and severity through changes in the number and activity of T_H -cell populations and through other means. For instance, stress has been shown to shift the relative proportion and trafficking of T_H1 and T_H2 cells to a T_H2 phenotype. In this article, the current understanding of interactions of the stress and immune systems and the physiologic and pathophysiologic implications of these interactions in human health and disease are reviewed. (*J Allergy Clin Immunol* 2000;106:S275-91.)

Key words: Allergic inflammation, hypothalamic-pituitary-adrenal (axis), norepinephrine, sickness syndrome, T_H cell

The neuroendocrine and immune systems play major roles in the adaptation and, hence, survival of an organism.^{1,2} Any stressor or threat to the stability or homeostasis of the internal milieu is counteracted by adaptive forces of the organism, collectively called the *adaptive response*. The central nervous system (CNS) effector of this response is the *stress system*, with its main components, the corticotropin-releasing hormone (CRH)/arginine-vasopressin (AVP) and locus ceruleus-norepinephrine (LC-NE)/autonomic (sympathetic) neurons of the hypothalamus and brain stem. These respectively regulate the peripheral activities of the hypothalamic-pituitary-adrenal (HPA) axis and the systemic/adreno-medullary sympathetic nervous systems (SNS). Activation of the HPA axis and LC-NE/autonomic system result in systemic elevations of glucocorticoids and catecholamines, respectively, which act in concert to maintain homeostasis. It is primarily through the stress system that stress influences the innate and specific immune response.

Abbreviations used

ACTH:	Adrenocorticotrophic hormone
APC:	Antigen-presenting cell
AVP:	Arginine vasopressin
cAMP:	Cyclic adenosine monophosphate
CGRP:	Calcitonin gene-related peptide
CNS:	Central nervous system
CRH:	Corticotropin-releasing hormone
HPA:	Hypothalamic-pituitary-adrenal (axis)
LC-NE:	Locus ceruleus-norepinephrine
NK:	Natural killer
SNS:	Sympathetic nervous system

Since the late 1930s, the adrenal glands were known to shrink the thymus and lymph nodes.² Subsequently, the glucocorticoids were found to inhibit lymphocyte proliferation, migration, and cytotoxicity and to suppress the secretion of certain cytokines, such as IL-2 and IFN- γ . These observations and the broad use of glucocorticoids as potent anti-inflammatory/immunosuppressant agents in the last 50 years led to the initial conclusion that stress was, in general, immunosuppressive.³ Recently, however, there has been convincing evidence that CRH, glucocorticoids, catecholamines, and other products of the stress system may influence the immune response in both directions, at both their baseline resting levels and/or at the elevated levels observed during stress. This new understanding helps explain some well-known, but often contradictory, effects of stress on the immune system and on the onset and course of certain infectious, autoimmune/inflammatory, allergic, and neoplastic diseases.

In the 1970s and 1980s, several groups demonstrated that newly described cytokines were involved in the stimulation of the brain, especially the HPA axis and the SNS.^{1,2} They showed that an immune and inflammatory response, associated with an increase in circulating inflammatory cytokines, stimulated plasma glucocorticoid concentrations, altered the activity of hypothalamic noradrenergic neurons, and decreased norepinephrine in the spleen. They also demonstrated that IL-1 could, to a great extent, reproduce the stimulatory effects of a severe inflammatory response on the HPA axis and the SNS.

In this overview, the current understanding of interactions of the stress and immune systems is presented, and

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the physiologic and pathophysiologic implications of these interactions in human health and disease are discussed. To limit the number of citations, several review articles containing many of the original references are included.

ORGANIZATION OF THE STRESS SYSTEM

The HPA axis and the SNS are peripheral limbs of the stress system, whose main function is to maintain basal and stress-related homeostasis.^{1,2} The central components of this system are located in the hypothalamus and the brain stem (Fig 1).² They include the parvocellular neurons of the paraventricular nuclei of the hypothalamus that release CRH and AVP, the CRH neurons of the paraventricular and parabrachial nuclei of the medulla, and the A1, A2, A3, and A6 (LC), mostly noradrenergic cell groups of the medulla and pons (the LC-NE system).

Each of the paraventricular nuclei has 3 parvocellular divisions: a medial group, which produces mostly CRH and projects and secretes into the hypophyseal portal system; an intermediate group, which produces mostly AVP and also projects and secretes into the hypophyseal portal system; and a lateral group, which produces primarily CRH and projects and innervates noradrenergic and other neurons of the stress system in the brain stem. Some parvocellular neurons contain and secrete both CRH and AVP, and this neural population increases with chronic stress. Other paraventricular CRH neurons project to and innervate proopiomelanocortin-containing neurons of the central stress system in the arcuate nucleus of the hypothalamus and the neurons of the pain control areas of the hindbrain and spinal cord (Fig 1).² Activation of the stress system leads to CRH-induced secretion of proopiomelanocortin-derived and other opioid peptides that enhance analgesia. These peptides simultaneously inhibit the activity of the stress system by suppressing CRH and norepinephrine secretion.

CRH stimulates the secretion of adrenocorticotrophic hormone (ACTH) by the corticotrophs of the anterior pituitary. Its effect on the pituitary is also permissive because, in the absence of CRH, very little ACTH secretion takes place. Arginine vasopressin alone has very little ACTH secretagogue activity but is a potent synergistic factor with CRH. Every hour, the parvocellular neurons secrete 2 or 3 mostly synchronous pulses of CRH and AVP into the hypophyseal portal system. In early morning, the amplitudes of these pulses are highest, which increases the amplitude and apparent frequency of ACTH and cortisol secretory episodes.⁴ The frequency appears to increase because previously undetectable pulses of ACTH and cortisol become measurable by standard assays. During acute stress, the amplitude of CRH and AVP pulses also increases, which results in increases in the amplitude and apparent frequency of ACTH and cortisol pulses. In this case, the stress system recruits additional secretagogues of CRH, AVP, or ACTH, such as magnocellular AVP and angiotensin II.

Circulating ACTH of pituitary origin is the key regulator of glucocorticoid secretion by the adrenal gland's *zona fasciculata*. Other hormones (including cate-

cholamines, neuropeptide Y and CRH that is derived from the adrenal medulla, and additional autonomic neural input to the adrenal cortex) also influence glucocorticoid secretion.⁴ The SNS, which originates in nuclei within the brain stem, gives rise to preganglionic efferent fibers that leave the CNS through the thoracic and lumbar spinal nerves ("thoracolumbar system"). Most of the sympathetic preganglionic fibers terminate in ganglia that are located in the paravertebral chains that lie on either side of the spinal column; the remaining preganglionic sympathetic neurons terminate in prevertebral ganglia, which lie in front of the vertebrae. From these ganglia, postganglionic sympathetic fibers run to the tissues that are innervated. Although most postganglionic sympathetic fibers release norepinephrine, there are also subpopulations of neurons that secrete other active substances, including neuropeptide Y and CRH. The adrenal medulla contains chromaffin cells, which are embryologically and anatomically homologous to those of the sympathetic ganglia and are derived from the neural crest. The adrenal medulla, unlike the postganglionic sympathetic nerve terminals, releases mainly epinephrine and to a lesser extent norepinephrine in an approximate ratio of 4:1. Typical preganglionic sympathetic nerve terminals, the main neurotransmitter of which is acetylcholine, innervate the chromaffin cells of the adrenal medulla.

Role of the stress system in maintaining basal and stress-related homeostasis

The stress system has a baseline, circadian activity, but also responds on demand to physical and emotional stressors.^{1,2} Both at rest and during stress, and primarily through CRH, glucocorticoids, and catecholamines, the stress system maintains basal and stress-related homeostasis. These substances are major regulators of behavior, fuel metabolism, cardiovascular function, and thermogenesis and adjust these functions according to needs. This system integrates and responds to a great diversity of distinct circadian, neurosensory, blood-borne, and limbic signals. These include humoral and neural signals from the immune and inflammatory reaction. Indeed, any immune challenge that threatens the stability of the internal milieu can be regarded as a stressor (ie, a stimulus to the organism that activates the stress system to help reestablish homeostasis).

Functionally, the CRH and LC-NE systems seem to participate in a positive, reverberating feedback loop so that the activation of 1 system also tends to activate the other.^{1,2} This includes projections of CRH-secreting neurons from the lateral paraventricular nuclei to the central sympathetic systems in the brain stem and, conversely, projections of catecholaminergic fibers from the LC-NE system, through the ascending noradrenergic bundle, to the paraventricular nuclei in the hypothalamus. Thus, CRH stimulates norepinephrine secretion through its specific receptors, whereas norepinephrine stimulates CRH secretion through primarily α_1 -noradrenergic receptors. Autoregulatory, ultrashort negative feedback loops are also present in these neurons, with CRH and norepinephrine collateral fibers acting in an inhibitory fashion on

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FIG 1. Major components of the central and peripheral stress system. The paraventricular nucleus and the locus ceruleus/noradrenergic system are shown with their peripheral limbs, the pituitary-adrenal axis, and the adrenomedullary and systemic sympathetic systems. The hypothalamic CRH and central noradrenergic neurons mutually innervate and activate each other, although they exert presynaptic autoinhibition through collateral fibers. AVP from the paraventricular nucleus synergizes with CRH on stimulating ACTH secretion. The cholinergic and serotonergic neurotransmitter systems stimulate both components of the central stress system, although the gamma aminobutyric acid/benzodiazepine (*GABA/BZD*) and arcuate nucleus proopiomelanocortin (*POMC*) peptide systems inhibit it. The latter is directly activated by the stress system and is important in the enhancement of the analgesia that takes place during stress. (From Chrousos GP. Seminars in Medicine of the Beth Israel Hospital, Boston: The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995;332:1351-62. Copyright © 1995 Massachusetts Medical Society. All rights reserved.)

presynaptic CRH and α_2 -noradrenergic receptors, respectively. The CRH, AVP, and noradrenergic neurons receive stimulatory input from the serotonergic, cholinergic, and histaminergic systems and inhibitory input from the gamma-aminobutyric acid/benzodiazepine and opioid peptide neuronal systems of the brain. The centrally secreted substance P has inhibitory actions on the hypothalamic CRH but not on AVP neurons and has stimulatory effects on the central noradrenergic system.

Activation of the stress system leads to adaptive behavioral and physical changes.^{1,2} Centrally, the behavioral changes include enhanced arousal and accelerated motor reflexes, better attention span and cognitive function, decreased feeding and sexual behavior, and

increased ability to withstand pain. Peripherally, the activation of the stress system results in increased sympathetic output (ie, an increase of the release of norepinephrine from the sympathetic nerve terminals and epinephrine/norepinephrine from the adrenal medulla and an increased secretion of glucocorticoids by the adrenal cortex). These changes are related to the physical adaptation that includes changes in cardiovascular function, intermediary metabolism, and modulation of the immune and inflammatory reaction.

Innervation of lymphoid organs

Sympathetic/noradrenergic and sympathetic/neuropeptide Y postganglionic nerve fibers innervate both

the smooth muscle of the vasculature and the parenchyma of specific compartments of primary and secondary lymphoid organs.⁵ These nerve fibers and their varicosities travel in plexuses that run adjacent to and along the blood vessels in these organs; hence, it is possible that both norepinephrine and neuropeptide Y released from these fibers play a role in controlling blood flow to these organs and the traffic of leukocytes within their vessels. However, some noradrenergic fibers that are not associated with blood vessels are present in the parenchyma of lymphoid tissues. Norepinephrine released from their nerve fibers may exert immunomodulatory roles by altering the activity of local leukocytes. Noradrenergic innervation of lymphoid tissues appears to be regional and specific; generally, zones of T cells, macrophages, and plasma cells are richly innervated, whereas nodular and follicular zones of developing or maturing B cells are poorly innervated.

The main target cells of the noradrenergic innervation of lymphoid organs appear to be immature and mature thymocytes, thymic epithelial cells, T lymphocytes, macrophages, mast cells, plasma cells, and enterochromaffin cells. Noradrenergic nerve fibers in the thymus are closely associated with mast cells within both the perivascular and parenchymal zones, which suggests a possible humoral role for norepinephrine and histamine in the maturation of T cells. Noradrenergic innervation is present early in development, and the arrival of the fibers generally precedes the development of the cellular compartment of the immune system, which suggests a role for norepinephrine and/or other products of the SNS in the development of this system.

In addition to the autonomic/sympathetic innervation, all lymphoid organs also receive sensory peptidergic innervation that is confined mostly to the parenchyma. The most abundant neuropeptides are the tachykinins, substance P, and neurokinin A; calcitonin gene-related peptide (CGRP); and vasoactive intestinal polypeptide/peptide histidine isoleucine. Double immunofluorescence reveals the coexistence of tachykinins with CGRP and tyrosine hydroxylase with neuropeptide Y. This coexistence pattern conforms to the general scheme described for the peripheral innervation of nonimmune organs.

A close spatial relationship between peptidergic nerve fibers and mast cells, T cells, or macrophages is observed in immune organs. Peptidergic nerves, however, are sparse in pure B-cell regions. Neuro-mast-cell contacts are present in lymphoid organs, except for the spleen. Mast cells bear receptors for and respond to substance P and CRH; both trigger the release of granules containing histamine, cytokines, and lipid mediators of inflammation, including leukotrienes. Norepinephrine, on the other hand, through the stimulation of α - or β -adrenoreceptors, stimulates or inhibits the release of granules that contain histamine and other proinflammatory substances from mast cells. Thus, apart from their direct immunomodulatory effects, substance P antidromically released from sensory nerves or norepinephrine and other active substances, such as CRH, released from postganglionic nora-

drenergic nerve terminals may exert indirect immunomodulatory effects through changes in mast-cell degranulation within the parenchyma of lymphoid organs.

Neuro-mast-cell connections, neuro-macrophage connections, and neuro-T-cell contacts are not restricted to the lymphoid organs and tissues but are also regularly encountered in most nonimmune tissues. Mast cells, T cells, and macrophages are regularly seen in contact with the terminals of peripheral nerves from the sympathetic and sensory ganglia. In the skin, postcapillary venules, macrophages, mast cells, and peptidergic nerves stained for tachykinins/CGRP form a typical quadrad; in the outer wall of larger blood vessels, the quadrad is joined by tyrosine hydroxylase/neuropeptide Y fibers. Further, close interrelations of tyrosine hydroxylase/neuropeptide Y and substance P/CGRP immunoreactive fibers are frequently observed in perivascular regions.

THE IMMUNE RESPONSE AND THE INFLAMMATORY REACTION

Any immune response, first, involves the recognition of a pathogen and, second, the mounting of a reaction against it. Broadly speaking, the different types of immune response fall into 2 categories: the innate (nonspecific) and the adaptive (specific) immune responses.⁶ Phagocytic cells (such as dendritic cells, monocytes, macrophages, and polymorphonuclear neutrophils) bind to microorganisms, internalize them, and kill them. Because phagocytic cells use primitive, nonspecific recognition systems that allow them to recognize and bind to a variety of microbial products and intracellular substances (such as hsp60 or HMG-1 released from necrotic tissues), they mediate innate immune responses, acting as a first line of defense. However, a subgroup of lymphocytes known as large granular lymphocytes or natural killer (NK) cells also have the capacity to recognize surface changes that occur on a variety of tumor cells or virally infected cells and to destroy these cells with nonspecific recognition systems. Both monocytes/macrophages and large granular lymphocytes may also recognize and destroy target cells (or pathogens) that are coated with specific antibody.

The phagocytic cells that initiate the innate immune response produce a set of proinflammatory cytokines (eg, TNF- α , IL-1, and IL-6) in the form of a cascade that amplifies the local inflammatory response, influences the adaptive immune response, and serves to signal the CNS of an inflammatory response.

Lymphocytes such as T lymphocytes (T cells) and B lymphocytes (B cells) are central components of the adaptive immune response because they recognize individual pathogens, whether they are inside host cells or outside in the tissue fluids or blood. B cells combat extracellular pathogens and their products by releasing antibodies that specifically recognize and bind target molecules or antigens. Antigens may be molecules on the surface of pathogens or soluble toxins produced by them. One group of lymphocytes, the T_H cells, exert regulatory function (ie, they interact with B cells and help them

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FIG 2. Major components and events of inflammation. **A**, Quiescent circulating leukocytes, local immune accessory cells, and the terminals of peripheral postganglionic sympathetic and sensory afferent neurons are shown. **B**, In the inflamed tissue, there are vasodilation, increased permeability of the vessel, and exudation of plasma. Activated leukocytes and endothelial cells express adhesion molecules and adhesion-molecule receptors. Cells attach to the vessel wall, and diapedesis takes place, with chemotaxis toward a chemokine gradient at the focus of inflammation. Activated circulating cells, migrant cells, local immune accessory cells, and peripheral nerves secrete cytokines, prostanoids, platelet-activating factor (PAF), neuropeptides, and other mediators of inflammation. Some of these substances (such as IL-6, leukotrienes, complement component 5 α , CRH, and transforming growth factor- β) have chemokinetic activity. Some substances (such as the inflammatory cytokines, TNF- α , IL-1, and IL-6) escape into the systemic circulation, causing systemic symptoms and activating the HPA axis. Because of such effects, these substances were historically referred to as "tissue corticotropin releasing factor." (From Chrousos GP. Seminars in Medicine of the Beth Israel Hospital, Boston: The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332:1351-62. Copyright © 1995 Massachusetts Medical Society. All rights reserved.)

divide, differentiate, and make antibody). T_H cells also interact with mononuclear lymphocytes and help them destroy intracellular pathogens. Another group of T cells, the T-cytotoxic cells, are responsible for the destruction of host cells that have been infected by viruses or other intracellular pathogens. T cells use a specific receptor, the T-cell antigen receptor, to recognize antigens, but only in association with familiar markers on host cells. This receptor is related both in structure and function to the surface antibody, which B cells use as their antigen receptors. T cells generate their effects either by releasing cytokines or by direct cell-cell interactions.

The cells of the immune system are widely distributed throughout the body, but if an infection occurs it is necessary to mobilize a large number of them at the site of infection.^{1,2} The process by which this occurs manifests itself as inflammation and includes an increased blood supply to the infected area by local vasodilatation and increased cap-

illary permeability to permit diapedesis of leukocytes and exudation of plasma that contains soluble mediators of immunity. The migration of leukocytes is assisted by a process of chemical attraction known as chemotaxis, exerted by substances called chemokines (Fig 2).

The cells that participate in the inflammatory reaction are monocytes, polymorphonuclear leukocytes (including neutrophils, basophils, and eosinophils), and lymphocytes, all recruited from the blood to the inflammatory site. Other cell participants include local immune accessory cells, such as endothelial cells, mast cells, tissue fibroblasts, and resident macrophages. In the earliest stages of inflammation, neutrophils are particularly prevalent, but in the later stages monocytes and lymphocytes take on a primary role. Local generation of secretory products (including cytokines, lipid mediators of inflammation, and neuropeptides) is crucial for further chemoattraction of cells and for the coordinated activa-

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FIG 3. Effect of CRH mast-cell histamine axis, glucocorticoids, and catecholamines on T_H1/T_H2 balance and, hence, cellular and humoral immunity. Stress and CRH influence immune/inflammatory and allergic responses by stimulating glucocorticoids, catecholamines and peripheral (immune) CRH secretion and by altering the production of key regulatory cytokines and histamine. *CRH is also released from sensory nerves on their activation. *Solid lines* represent stimulation; *dashed lines* represent inhibition. NA, Nor-adrenaline; GR, glucocorticoid receptor; Tc, T-cytotoxic cell; Eo, eosinophil; B, B cell. (Reprinted from Elenkov IJ, Chrousos GP. Stress Hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. Trends Endocrinol Metab 1999;10:359-68. Copyright 1999, with permission from Elsevier Science.)

tion of the effector cells. In most instances, these events are clinically undetectable. Occasionally, however, clinical inflammation occurs, which generates high concentrations of local and circulating levels of cytokines and other mediators of inflammation that are associated with systemic illness manifestations and activation of the stress system.

The postganglionic sympathetic neurons and the sensory afferent fibers of the peripheral nervous system also influence inflammation (Fig 2).² Locally, the neuropeptide CRH and the neurotransmitter norepinephrine, released from the postganglionic sympathetic nerve fibers, exert mostly proinflammatory and anti-inflammatory effects, respectively. The sensory fibers sense the local threat and not only send signals to the CNS but also antidromically secrete proinflammatory or anti-inflammatory substances (such as the neuropeptides substance P or somatostatin, respectively) at the site of inflammation.

Role of T_H1 and T_H2 cells and Type 1 and Type 2 cytokines in the regulation of cellular and humoral immunity

Immune responses are regulated by antigen-presenting cells (APCs; such as monocytes/macrophages, dendritic cells, and other phagocytic cells that are components of innate immunity) and by the recently described lymphocyte subclasses T_H1 and T_H2 that are components of adaptive immunity. T_H1 cells primarily secrete IFN- γ , IL-2, and TNF- α , which promote cellular immunity, whereas T_H2 cells secrete a different set of cytokines, primarily IL-4, IL-10, and IL-13, which promote humoral immunity (Fig 3).⁶

Naive CD4⁺ (antigen-inexperienced) T_H0 cells are clearly bipotential and serve as precursors of T_H1 and T_H2 cells. Among the factors currently known to influence the differentiation of these cells toward T_H1 or T_H2 , cytokines produced by cells of the innate immune system are the

most important. Thus, IL-12, produced by activated monocytes/macrophages or other APCs, is a major inducer of T_H1 differentiation and hence of cellular immunity. This cytokine acts in concert with NK-derived IFN- γ to further promote T_H1 responses. APC-derived IL-12 and TNF- α , in concert with NK cells and T_H1 cell-derived IFN- γ , stimulate the functional activity of T-cytotoxic cells, NK cells, and activated macrophages (ie, the major components of cellular immunity). All 3 cytokines (IL-12, TNF- α , and IFN- γ) also stimulate the synthesis of nitric oxide and other inflammatory mediators that drive chronic delayed-type inflammatory responses.

T_H1 and T_H2 responses are mutually inhibitory. Thus, IL-12 and IFN- γ inhibit T_H2 and, vice versa, IL-4 and IL-10 inhibit T_H1 responses. IL-4 and IL-10 and, in the case of atopy, IL-5 promote humoral immunity by stimulating the growth and activation of mast cells and eosinophils, the differentiation of B cells into antibody-secreting B cells, and B-cell immunoglobulin switching to immunoglobulin E. Importantly, these cytokines inhibit macrophage activation, T-cell proliferation, and the production of proinflammatory cytokines. Thus, IL-4 and IL-10 are major anti-inflammatory cytokines (Fig 3).⁶

EFFECTS OF THE HPA AXIS AND THE SNS ON THE IMMUNE AND INFLAMMATORY REACTIONS

Adrenocortical hormones

The anti-inflammatory and immunosuppressive properties of glucocorticoids exerted through their ubiquitous intracellular receptors make them invaluable therapeutic agents in numerous diseases.⁷ The glucocorticoid receptor is a 777-amino-acid cytoplasmic protein with 3 major functional domains and several subdomains. The carboxyterminal region binds glucocorticoid, and the middle portion domain binds to specific sequences of DNA in the regulatory regions of glucocorticoid-responsive genes (glucocorticoid-responsive elements).

Glucocorticoids influence the trafficking of leukocytes and inhibit many functions of leukocytes and immune accessory cells. They suppress the immune activation of these cells, inhibit the production of cytokines and other mediators of inflammation, and cause cytokine resistance. Subgroups of T cells are particularly affected by glucocorticoids. Thus, these hormones suppress T_H1 function and stimulate apoptosis of eosinophils and certain groups of T cells. Glucocorticoids also inhibit the expression of adhesion molecules and their receptors on the surface of immune and other cells and ameliorate the chronic-phase reaction. All of these effects depend on altering the transcription rates of glucocorticoid-responsive genes or changing the stability of the messenger RNA of several proteins involved in inflammation. For instance, glucocorticoids suppress the production of IL-6 and IL-1 by decreasing both the transcription rate of the genes for these interleukins and the stability of their messenger RNA.

Among the many proteins regulated by glucocorticoids are the phospholipase A2, cyclooxygenase 2, and

inducible nitric oxide synthase 2 genes. Suppression of these proteins decreases the production of prostanooids, platelet-activating factor, and nitric oxide, 3 key molecules in the inflammatory response. The activated glucocorticoid receptor also inhibits the proinflammatory activity of many growth factors and cytokines by directly interacting with and blocking the third messenger systems for these hormones. These include the transcription factors AP-1, nuclear factor-kappa-B, and cyclic adenosine monophosphate (cAMP)-responsive element binding protein. In a mutual fashion, elevated intracellular concentrations of these factors prevent the activated glucocorticoid receptor from exerting its effects on the genome.

Several circadian immune functions cause disease-associated diurnal changes that correspond to plasma glucocorticoid levels.² For example, the delayed hypersensitivity reaction, which is particularly sensitive to glucocorticoids, is greatest in the evening when glucocorticoids are low and least in the morning when they are high. The same is true for the cytokine IL-6, whose levels in plasma have a circadian rhythm, with peaks in the evening and early morning hours.

Catecholamines

Lymphocyte trafficking and circulation are under the influence of the SNS and catecholamines.^{2,5,6} In the short term (<30 minutes), catecholamines mobilize NK cells from depots, whereas in the long term (chronic), catecholamines decrease the number of lymphocytes, particularly NK cells, in the peripheral blood. Catecholamines or β -adrenoreceptor agonists inhibit the T-cell proliferation induced by mitogens. This is usually accompanied by an increase in cAMP in the lymphocytes, and the amount of this that is produced by T cells that are stimulated with isoproterenol (a β -adrenoreceptor agonist) is proportional to the degree of inhibition of the proliferation. β -adrenoreceptor agonists exert similar inhibitory effects on the proliferative response of human highly purified T cells that are stimulated with immobilized anti-CD3 monoclonal antibody through the CD3/T-cell antigen receptor complex.

In vitro and in vivo studies reveal that catecholamines both acutely and chronically mediate the inhibition of NK-cell activity. Central administration of CRH (known to increase the sympathetic autonomic outflow) is accompanied by decreased NK activity in the periphery, an effect that is independent of adrenocortical activation. This effect of central CRH is also rapid; within 20 minutes of infusion, lytic values of splenic NK cells decline by nearly 50%, whereas the cytotoxicity of peripheral NK cells is reduced within 1 hour. Moreover, several lines of evidence suggest that stress, which is accompanied by increased levels of peripheral catecholamines, inhibits several components of cellular immunity and particularly NK-cell activity, an effect that is mediated mainly by the CRH-SNS axis. In animals, the central application of anti-CRH antibodies completely blocks the inhibitory effect of footshock stress on NK activity. It appears that NK cells are the cells most sensitive to the

suppressive effect of stress, and, not surprisingly, in many studies NK-cell activity has become a bona fide index of stress-induced suppression of cellular immunity. Apart from a direct, acute effect, catecholamines may indirectly, chronically suppress NK activity; their potent inhibition of the production of IL-12 and IFN- γ is essential for NK activity.

Catecholamines appear to have both inhibitory and stimulatory effects on macrophage activity. This process is influenced by several factors, such as the availability of type 1/proinflammatory cytokines; the presence or absence of antigen; the presence in the microenvironment of proinflammatory mediators such as substance P; peripheral (immune) CRH and histamine, released from the sensory and postganglionic-sympathetic neurons or mast cells, respectively; and the state of activation or differentiation of macrophages, which may determine the β -adrenoreceptors responsiveness and the expression of α -adrenoreceptors. Catecholamines also exert enhancing effects on the initiation of T-cytotoxic responses, in contrast with the inhibition of effector T-cytotoxic-cell function. Catecholamines inhibit both neutrophil phagocytosis and the release of lysosomal enzymes from neutrophils. Furthermore, the superoxide generation and formation of oxygen radicals that play an important microbicidal role are suppressed at nanomolar concentrations of epinephrine, an effect mediated by β_2 -adrenoreceptors.

Stress hormones suppress cellular and potentiate humoral immunity

Effects of glucocorticoids. Glucocorticoids suppress the production of TNF- α , IFN- γ , and IL-2 in vitro and in vivo in animals and humans.² As recently shown, glucocorticoids also act through their classic cytoplasmic/nuclear receptors on APCs to suppress the production of IL-12, the main inducer of T_H1 responses, in vitro and ex vivo.⁶ Because IL-12 is extremely potent in the enhancement of IFN- γ and the inhibition of IL-4 synthesis by T cells, the inhibition of IL-12 production may represent a major mechanism through which glucocorticoids affect the T_H1/T_H2 balance. Thus, glucocorticoid-treated monocytes/macrophages produce significantly less IL-12, which leads to a decreased capacity of these cells to induce IFN- γ production by antigen-primed CD4⁺ T cells. The same treatment of monocytes/macrophages is also associated with an increased production of IL-4 by T cells, probably resulting from disinhibition of the suppressive effects of IL-12 on T_H2 activity (Fig 3).⁶

Furthermore, glucocorticoids potently down-regulate the expression of IL-12 receptors on T and NK cells. This explains why human peripheral blood mononuclear cells that are stimulated with immobilized anti-CD3 lose their ability to produce IFN- γ in the presence of glucocorticoids. Thus, although glucocorticoids may have a direct suppressive effect on T_H1 cells, the overall inhibition of IFN- γ production by these cells appears to result mainly from the inhibition of IL-12 production by APCs and from the loss of IL-12 responsiveness of NK and T_H1 cells.

It is particularly noteworthy that glucocorticoids have no effect on the production of the potent anti-inflammatory cytokine IL-10 by monocytes; yet, lymphocyte-derived IL-10 production is up-regulated by glucocorticoids. Thus, rat CD4⁺ T cells pretreated with dexamethasone exhibit increased levels of messenger RNA for IL-10. Similarly, during experimental endotoxemia or cardiopulmonary bypass or in patients with multiple sclerosis who experience an acute relapse, treatment with glucocorticoids is associated with increased plasma IL-10 secretion. This may have resulted from a direct stimulatory effect of glucocorticoids on T-cell IL-10 production and/or from disinhibition of the restraining inputs of IL-12 and IFN- γ on monocyte/lymphocyte IL-10 production.

Effects of catecholamines. Catecholamines drive a T_H2 shift at the level of both APCs and T_H1 cells (Fig 3).⁶ We recently demonstrated that noradrenaline and adrenaline potently inhibited or enhanced the production of IL-12 and IL-10, respectively, in human whole blood cultures that were stimulated with lipopolysaccharide ex vivo.⁸ These effects are mediated by stimulation of β -adrenoreceptors, as evidenced by the fact that they are completely prevented by propranolol, a β -adrenoreceptor antagonist. Our findings were subsequently extended by other laboratories that showed that nonselective β - and selective β_2 -adrenoreceptor agonists inhibited the production of IL-12 in vitro and in vivo. In conjunction with their ability to suppress IL-12 production, β -adrenoreceptor agonists inhibited the development of T_H1 cells and promoted T_H2 cell differentiation.

β -adrenoreceptors are expressed on T_H1 cells but not on T_H2 cells. This may provide an additional mechanistic basis for a differential effect of catecholamines on T_H1/T_H2 functions. In fact, in both murine and human systems β -adrenoreceptor agonists inhibit IFN- γ production by T_H1 cells but do not affect IL-4 production by T_H2 cells. Importantly, the differential effect of catecholamines on T_H1/T_H2 cytokine production also operates in vivo. Thus, the increasing sympathetic outflow in mice by selective β -adrenoreceptor antagonists or the application of β -adrenoreceptor agonists results in the inhibition of lipopolysaccharide-induced TNF- α and IL-12 production. In humans, the administration of the β -adrenoreceptor agonist salbutamol results in the inhibition of IL-12 production ex vivo, and the acute brain trauma that is followed by massive release of catecholamines triggers the secretion of substantial amounts of systemic IL-10.

Catecholamines exert inhibition on the production of proinflammatory cytokines in vivo. The application of propranolol results in substantial increases of lipopolysaccharide-induced secretion of TNF- α and IL-12 in mice. Thus, systemically, both glucocorticoids and catecholamines inhibit and stimulate T_H1 and T_H2 cytokine secretion, respectively, to cause selective suppression of cellular immunity and a shift toward T_H2 -mediated humoral immunity. This is further substantiated by studies that show that stress hormones inhibit effector function of cellular immunity components (ie, the activity of NK and T-cytotoxic cells and activated macrophages).

Because the response to β -adrenoreceptor agonist stimulation wanes during maturation of the human monocyte, it is possible that in certain compartments of the body, the α -adrenoreceptor-mediated effect of catecholamines becomes transiently dominant. Through this mechanism, catecholamines may actually enhance local cellular immune responses in a transitory fashion. This is further substantiated by the finding that catecholamines potentiate the production of IL-8 from peripheral blood mononuclear cells and epithelial cells of the lung, thereby promoting the recruitment of polymorphonuclear leukocytes to this organ. The "paradoxical" stress-induced potentiation of inflammation in the lung may explain the reason that the "adult respiratory distress" syndrome develops frequently in patients with major infections that are associated with profound activation of the stress system. In summary, although stress hormones suppress T_H1 responses and proinflammatory cytokine secretion and enhance T_H2 responses systemically, they may differentially affect certain local responses. Further studies are needed to address this question.

The CRH-mast-cell-histamine axis

Central, hypothalamic CRH influences the immune system indirectly through activation of the end products of the peripheral stress response (ie, glucocorticoids and catecholamines). CRH, however, is also secreted peripherally at inflammatory sites (peripheral or immune CRH) and influences the immune system directly through local modulatory actions.² We first localized immunoreactive CRH in the inflamed tissues of animals with experimental carageenan-induced subcutaneous aseptic inflammation, streptococcal cell wall- and adjuvant-induced arthritis, and retinol-binding protein-induced uveitis, and in human tissues from patients with various autoimmune/inflammatory diseases, including rheumatoid arthritis, autoimmune thyroid disease, and ulcerative colitis. The demonstration of CRH-like immunoreactivity in the dorsal horn of the spinal cord, dorsal root ganglia, and sympathetic ganglia supports the hypothesis that most immune CRH in early inflammation is from the peripheral nerve rather than from immune cell origin.

Peripheral CRH has proinflammatory, vascular permeability-enhancing and vasodilatory actions. Thus, systemic administration of specific CRH antiserum blocks the inflammatory exudate volume and cell number in carageenan-induced inflammation and retinol-binding protein-induced uveitis and inhibits stress-induced intracranial mast-cell degranulation. In addition, CRH administration to humans or nonhuman primates causes major peripheral vasodilation, which manifests as flushing and increased blood flow and hypotension. Intradermal CRH injection induces a marked increase in vascular permeability and mast-cell degranulation.⁹ Importantly, this effect is blocked by a CRH type 1 receptor antagonist and is stronger than the effect of an equimolar concentration of C48/80, a potent mast-cell secretagogue.

Therefore, it appears that the mast cell is a major target of immune CRH. This has an anatomic prerequisite; in

blood vessels, periarterial sympathetic plexuses are closely associated with mast cells that line the perivascular regions; plexuses of nerve fibers (noradrenergic and peptidergic) within lymphoid parenchyma are also closely associated with clusters of mast cells. Histamine, a major product of mast-cell degranulation, is a well-recognized mediator of acute inflammation and allergic reactions. These actions are mainly mediated by the activation of H_1 histamine receptors and include vasodilation, increased permeability of the vessel wall, edema, and bronchoconstriction. Thus, it is conceivable that CRH activates mast cells through a CRH receptor type 1-dependent mechanism, which leads to the release of histamine and other contents of the mast-cell granules that subsequently cause vasodilation, increased vascular permeability, and other manifestations of inflammation (Fig 3).⁶

Over the last 10 to 15 years, strong evidence has emerged that histamine may have important immunoregulatory functions through H_2 receptors that are expressed on immune cells. We have recently found that histamine, through the stimulation of H_2 receptors on peripheral monocytes and the subsequent elevation of cAMP, inhibits the secretion of human IL-12 and stimulates the production of IL-10.¹⁰ Our data are consistent with previous studies that show that histamine, through H_2 -receptors, also inhibits TNF- α production from monocytes and IFN- γ production by T_H1 -like cells but has no effect on IL-4 production from T_H2 clones. Thus, histamine, similarly to catecholamines, appears to drive a T_H shift at the level of both APCs and T_H1 cells. The activation of the CRH-mast-cell-histamine axis through stimulation of H_1 -receptors may induce acute inflammation and allergic reactions, whereas the activation of H_2 -receptors may induce the suppression of T_H1 responses and a T_H2 shift (Fig 3).⁶

Generalizations of the effects of stress on the immune and inflammatory response

The evidence, which was accumulated over the last decade, strongly suggests that stress hormones differentially regulate T_H1/T_H2 patterns and T_H1/T_H2 cytokine secretion. Although interest in the T_H2 response was initially directed at its protective role in helminthic infections and its pathologic role in allergy, this response may have important regulatory functions in countering the tissue-damaging effects of macrophages and T_H1 cells. Thus, an excessive immune response through activation of the stress system and, hence, through glucocorticoids and catecholamines suppresses the T_H1 response and causes a T_H2 shift. This may protect the organism from "overshooting" by producing type 1/proinflammatory cytokines and other products of activated macrophages with tissue-damaging potential.

Locally, stress may exert pro- or anti-inflammatory effects. This may be influenced by several factors (such as the organ involved, the nature of the response, the presence or absence of antigen, the nature of antigen, and/or the presence and relative expression of particular receptor subtypes on the surface of immune cells [eg, β - versus α -adrenergic or H_1 - versus H_2 -histaminergic

TABLE I. Cytokines and other mediators of inflammation that influence the HPA axis

Inflammatory cytokines/chemokines
TNF- α
IL-1 α , IL-1 β
IL-6
IL-8
Other cytokines
IFN- α
IFN- γ
IL-2
IL-12
Growth factors
Epidermal growth factor
Transforming growth factor- β
Lipid mediators
Prostanoids
Platelet-activating factor

receptors]). Despite some stereotyping, stress is not a uniform, nonspecific reaction; this includes its effects on the immune and inflammatory reaction. Indeed, different types of stressors with their own central neurochemical and peripheral neuroendocrine “signatures” might have different effects on the immune response.

EFFECTS OF THE IMMUNE AND INFLAMMATORY REACTION ON THE HPA AXIS AND THE SNS

The last 2 to 3 decades provided evidence that, during an immune response, certain cytokines can signal the CNS, which, through a complex CRH-dependent pathway triggers the activation of both the HPA axis and the SNS.² Most of the HPA axis-stimulating activity in plasma comes from 3 cytokines (TNF- α , IL-1, and IL-6), which are produced at inflammatory sites and elsewhere in response to inflammation. In most situations, TNF- α appears first, followed by simultaneous secretion of IL-1 and IL-6. All 3 cytokines stimulate their own secretion from the cells that produce them. In addition, TNF- α and IL-1 stimulate the secretion of IL-6, whereas IL-6 inhibits the secretion of TNF- α and IL-1. IL-6 acts synergistically with glucocorticoids in stimulating the production of acute phase reactants. The secretion of systemic IL-6 is also increased during stress of noninflammatory etiology, presumably stimulated by stress-induced catecholamines through a β_2 -adrenergic receptor mechanism.

All 3 inflammatory cytokines independently activate the HPA axis; in combination, their effects are synergistic. Activation can be blocked with CRH-neutralizing antibodies, glucocorticoids, and prostanoid synthesis inhibitors. All 3 cytokines also directly stimulate CRH secretion in rat hypothalamic explants, an effect that can be inhibited *in vitro* by glucocorticoids and prostanoid synthesis inhibitors. The 3 inflammatory cytokines also potentiate the stimulatory effect of bacterial lipopolysaccharide on the HPA axis. Antibodies to IL-6 almost com-

pletely inhibit this effect, which suggests a central role for IL-6 in axis stimulation.

Elevations in ACTH and cortisol that were attained after IL-6 dosing in humans are well above those observed with maximal stimulating doses of CRH, which suggests that IL-6, in addition to CRH, stimulates parvocellular AVP and other ACTH secretagogues.¹¹ Levels of ACTH are already maximal at doses of IL-6 that do not increase peripheral AVP levels. At higher doses, however, IL-6 causes peripheral elevations in AVP levels, which indicates that this cytokine can also activate magnocellular AVP-secreting neurons. These data suggest that IL-6 elevations may be a common etiologic factor in the syndrome of inappropriate secretion of AVP that was observed in diverse states (such as infectious or inflammatory diseases or trauma).

The HPA axis and the SNS are involved in a long feedback loop between the immune system and the CNS. The afferent limb of this loop seems to operate by blood-borne cytokines, which either through the circulation or through the afferents of the vagus nerve, activate the central components of the stress system. How inflammatory cytokines reach the hypothalamic CRH and AVP neurons is unclear, given that the blood-brain barrier protects the cellular bodies of both kinds of neurons. The cytokines may stimulate endothelial and glial cells to secrete prostanoids, IL-6, and other mediators of inflammation, which reach the CRH and AVP neurons in a cascade-like fashion. Alternatively, a special transport system may be present for 1 or more of the inflammatory cytokines. The inflammatory cytokines may directly activate the terminals of the CRH and AVP neurons in the median eminence, which is outside the blood-brain barrier.

Inflammation may also activate the HPA axis indirectly by the stimulation of the central noradrenergic stress system through cytokines and other mediators, which act first on stress system neurons of the area postrema that lie outside the blood-brain barrier or on neuron bodies inside the barrier through the endothelial-glial-neuronal cascade mentioned earlier. In addition, nociceptive, visceral, and somatosensory afferent neurons of the peripheral nervous system from inflammatory sites acutely stimulate the noradrenergic and CRH stress systems through an ascending neural spinal or cerebral nerve route. In fact, several lines of evidence indicate that certain cytokines (such as IL-1 and IFN- α) stimulate both the central and peripheral components of the SNS. Thus, the administration of IL-1 in the periphery increases the turnover of norepinephrine in the hypothalamus and increases peripheral norepinephrine and epinephrine plasma levels. Intracerebroventricular and peripheral injection of IFN- γ or IL-1 produces a long-lasting increase in the sympathetic activity of the splenic nerve and an increased turnover of norepinephrine in the spleen.

In addition to their acute effects on the hypothalamus, the inflammatory cytokines can apparently directly stimulate pituitary ACTH and adrenal cortisol secretion at high concentrations or with adequate time for interaction with these tissues.^{2,11} Normally, the anterior pituitary and

adrenal glands produce IL-6, TGF- β , and other cytokines, which may influence local hormone production. However, these cytokines may not always stimulate the pituitary gland or the adrenal cortex. IL-6, TNF- α , and IFN- γ inhibit the stimulatory effect of CRH on anterior pituitary cell cultures, whereas TNF- α and TGF- β are potent inhibitors of ACTH-induced cortisol production by cultured adrenocortical cells.

Other inflammatory mediators and cytokines (including IFN- γ , IL-2, epidermal growth factor, TGF- β , prostanoids, and platelet-activating factor) may also participate in the modulation of the HPA axis activity by inflammation (Table I). The interferons, IL-2, and IL-12 may do so indirectly by causing the secretion of inflammatory cytokines. Prostanoids and platelet-activating factor, however, are primarily autacoid amplifiers of hypothalamic CRH and AVP secretion. Receptors for these substances are present in the paraventricular nuclei, and CRH and AVP neurons respond to them.

Certain cytokines or combinations of cytokines have been shown to cause their target tissues to become resistant to glucocorticoids.^{2,7} IL-2 and IL-4 together cause glucocorticoid resistance in T cells by markedly decreasing the affinity of the glucocorticoid receptor for its ligand by a mechanism that is currently unclear. In addition, changes in the intracellular metabolism of cortisol into less active or inactive metabolites in cells of the immune system alter the sensitivity of these cells to glucocorticoids.

Inflammatory stress: A compound syndrome

The last 15 years have provided evidence that certain cytokines, particularly the proinflammatory ones (eg, TNF- α , IL-1, and IL-6), activate both the HPA axis and the LC-NE/SNS system (ie, the key components of the classic stress response).^{2,11} Moreover, these cytokines induce anorexia/nausea, fatigue, social withdrawal and/or depressive affect, hyperalgesia with or without headache, somnolence, sleep disturbances, temperature elevation or fever, and increases of the basal metabolic rate, adaptive changes collectively referred to as "sickness syndrome." These cytokines also activate the hepatic and other tissue synthesis of acute-phase proteins (such as C-reactive protein, cell-adhesion molecules, fibrinogen, and plasminogen activator inhibitor-1, another adaptive phenomenon referred to as the "acute phase reaction"). Stress that is associated with an immune challenge has been called "immune stress" or "inflammatory stress," which is a combination of the sickness and classic stress syndromes, along with their effects on the pain/afferent neural systems and the acute phase reaction (Table II; Fig 4).

DISTURBANCES IN THE INTERACTION BETWEEN THE STRESS AND IMMUNE SYSTEMS

Defects of the HPA axis and/or SNS

Disturbances in the feedback between the HPA axis and the immune and inflammatory reaction have been observed in animals and humans (Table III).² An exces-

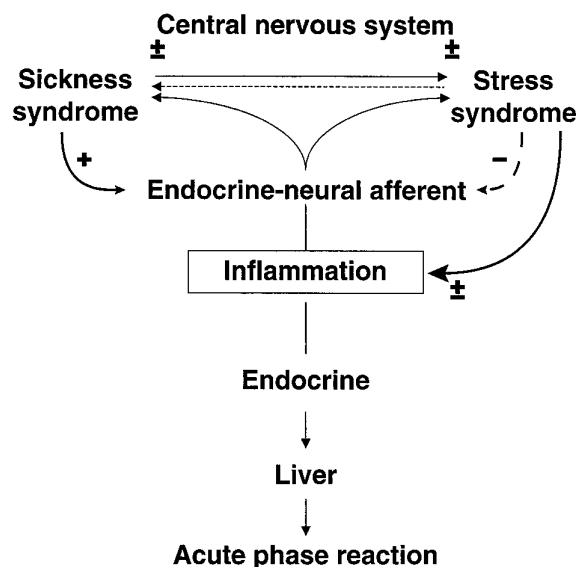


FIG 4. During the immune and inflammatory response, 2 major biologic programs are activated: the sickness and stress syndromes. These programs exert synergistic or antithetical effects on each other and influence both the pain/neural afferent program and the acute phase reaction in opposite or similar directions, respectively.

sive HPA response to inflammation can mimic the stress or hypercortisolemic state, increase susceptibility to certain infectious agents and tumors, and increase resistance to autoimmune or inflammatory disease. Conversely, a defective HPA-axis response can mimic the glucocorticoid-deficient state and cause resistance to infections and neoplasms and increased susceptibility to autoimmune and inflammatory disease. Indeed, such properties were identified in Fischer and Lewis rats, 2 highly inbred strains selected for their resistance (Fischer) or susceptibility (Lewis) to inflammatory disease. In the Lewis rat, the responsiveness of the HPA axis to inflammatory stimuli is decreased, whereas in the Fischer rat HPA-axis responsiveness to the same stimuli is increased.

Lewis rats are susceptible to a host of inflammatory diseases, such as a rheumatoid arthritis-like syndrome in response to streptococcal cell-wall peptidoglycan, uveitis in response to immunization with retinol-binding protein, and encephalomyelitis in response to myelin basic protein. Fischer rats, by contrast, resist these experimentally induced diseases. The defect in the Lewis rat is localized to the hypothalamic CRH neuron, which is globally defective in its response to all stimulatory neurotransmitters. The overall HPA-axis response to stress is decreased in the Lewis rat; in addition, these animals exhibit chronic elevations in vasopressin and behaviors reminiscent of atypical depression in humans, a state characterized by low hypothalamic CRH secretion.

Do the abnormalities in Lewis rats have parallels in humans? A subgroup of patients with active rheumatoid arthritis might qualify.² These patients have low or nor-

TABLE II. Inflammatory stress syndrome as a compound of 2 major biologic programs of adaptation

Sickness syndrome	Classic stress syndrome
Anorexia/nausea	Anorexia/stimulation of appetite*
Fatigue, social withdrawal and/or depressed affect	Motivation/stimulated affect
Somnolence	Arousal
Hyperalgesia	Analgesia
Headache	
Elevated temperature, fever	Antipyretic
Increased metabolic rate	Increased metabolic rate/return to normal*
Acute phase reaction++++	Acute phase reaction+
Molecular effectors	
Inflammatory cytokines/mediators	CRH, AVP, glucocorticoids, catecholamines, immune CRH

*Initially, stimulation through CRH and catecholamines; then inhibition by glucocorticoids.

++++, large response.

+, small response.

mal circadian concentrations of ACTH and cortisol despite elevated plasma concentrations of IL-1 β and IL-6.¹² Such patients have a poor response to stress that is associated with major surgery (such as large joint replacement), despite dramatic postoperative elevations in IL-1 β and IL-6 levels. Like Lewis rats, these patients also have consistently elevated levels of circulating AVP. Similar to Lewis rats with streptococcal cell-wall peptidoglycan-induced arthritis, the inflamed joints of these patients have markedly elevated concentrations of immunoreactive CRH. None of these abnormalities of the HPA axis was present in control patients with osteomyelitis (inflammatory disease) or degenerative osteoarthritis.

A key question about human rheumatoid arthritis is whether the hyporesponsiveness of the HPA axis is genetically constitutional or the result of a particular type of chronic inflammation or both. To date, the data point to a genetic disturbance that defines increased susceptibility. Prospective studies of families with autoimmune inflammatory disease should test this hypothesis using a quantifiable benign inflammatory stimulus (such as human recombinant IL-6). Other examples suggest that a defective HPA axis increases susceptibility to autoimmune disease or increased immune reactivity (Table III).² Given the many behavioral effects of the inflammatory cytokines and CRH, it is not surprising that fatigue, dysrhythmia, irritability, or even frank depression are frequent in many of these low CRH states in which one would expect amplification of some sickness syndrome manifestations.

Defects of the glucocorticoid target tissues

Glucocorticoid hypersensitivity of the immune system can mimic the immunosuppression of hypercortisolism, whereas glucocorticoid resistance of the immune system may result in excessive immune and inflammatory activity in target tissues (Table III).^{2,7} Six diseases illustrate this mechanism. In rheumatoid arthritis, the concentration of glucocorticoid receptors in circulating leukocytes

is reduced by approximately 50%. This phenomenon cannot be attributed to hypercortisolism. Leukocyte resistance to glucocorticoids also occurs in steroid-resistant asthma. Most patients with this disorder have marked but reversible decreases in affinity of glucocorticoid receptors in T lymphocytes. This suggests that steroid-resistant asthma is an acquired problem, probably associated with elevations of transcription factors (such as AP-1, NF- κ B, and cAMP-responsive element-binding protein), which interact with and neutralize activated glucocorticoid receptors. However, in a small subgroup of patients, glucocorticoid receptor concentrations are irreversibly decreased in all leukocyte subtypes, which suggests a congenital syndrome.

In some patients with terminal acquired immunodeficiency syndrome, leukocytes also have a marked decrease in the affinity of glucocorticoid receptors for cortisol. In these patients, glucocorticoid resistance may be generalized, because there are signs of glucocorticoid deficiency, including postural hypotension and hyponatremia, despite elevated levels of corticotropin and cortisol. A fourth disease in which the reduced expression of glucocorticoid receptors and glucocorticoid resistance may have a role is degenerative osteoarthritis. Osteoarthritic chondrocytes contain approximately one half of the glucocorticoid receptors of normal chondrocytes and resist dexamethasone-induced suppression of metalloproteinase synthesis. Metalloproteinase participates in the limited inflammatory destruction of the cartilage in the joints of patients with osteoarthritis. Finally, glucocorticoid resistance has also been observed in patients with Crohn's disease and in patients with systemic lupus erythematosus.

Stress-induced T_H2 shift: Clinical implications

A major factor that governs the outcome of infectious diseases is the selection of T_H1- versus T_H2-predominant adaptive responses during and after the initial invasion of the host.⁶ Stress and a stress-induced T_H2 shift may have a profound effect on the susceptibility of the organism to the course of the infection, the defense against which is

TABLE III. States potentially associated with suppression or activation of the immune and inflammatory reaction through defects in the HPA axis or its target tissues

Table available in print only

primarily through cellular immunity mechanisms. For instance, cellular immunity, and particularly IL-12 and IL-12-dependent IFN- γ secretion in humans, seems essential in the control of mycobacterial infections and may be of importance in the control of *Helicobacter pylori* infections.

HIV-infected patients have IL-12 deficiency, and their disease progression has been correlated with a T_H2 shift.⁶ The sympathetic/noradrenergic innervation of lymphoid tissue may be particularly relevant to HIV infection because lymphoid organs represent the primary site of HIV pathogenesis. Noradrenaline, the major sympathetic neurotransmitter released locally in lymphoid organs, directly accelerates HIV-1 replication in acutely infected human peripheral blood mononuclear cells. The effect of noradrenaline on viral replication is transduced through the β -adrenoreceptor–adenylyl cyclase–cAMP–protein kinase A signaling cascade. The HIV-1 itself may contribute to the induction of intracellular cAMP through an immunosuppressive retroviral envelope peptide that elicits a shift in the cytokine balance toward the suppression of cell-mediated immunity.

Progression of HIV infection is also characterized by increased cortisol secretion in both the early and late

stages of the disease. Progressively (albeit mildly) increasing glucocorticoid production, triggered by the chronic infection, was recently proposed to contribute to HIV progression. Kino et al¹³ found that 1 of the HIV-1 accessory proteins, Vpr, acts as a potent coactivator of the host glucocorticoid receptor, rendering lymphoid cells hyperresponsive to glucocorticoids. On the one hand stress hormones suppress cellular immunity and directly accelerate HIV replication, whereas on the other hand the virus itself suppresses cell-mediated immunity using the same pathways by which stress hormones, including catecholamines and glucocorticoids, alter the T_H1/T_H2 balance.

Major injury (serious traumatic injury and major burns) or major surgical procedures often lead to severe immunosuppression that contributes to delayed wound healing and infectious complications and, in some cases, to sepsis, the most common cause of late death after trauma.⁶ A strong stimulation of the SNS and the HPA axis correlates with the severity of both cerebral and extracerebral injury and an unfavorable prognosis. The suppressed cellular immunity is associated with the diminished production of IFN- γ and IL-12 and the increased production of IL-10 (ie, a T_H2 shift).

In rheumatoid arthritis, multiple sclerosis, type-1 diabetes mellitus, autoimmune thyroid disease, and Crohn's disease, the T_H balance is skewed towards T_H1 and an excess of IL-12 and TNF- α production, whereas T_H2 activity and the production of IL-10 are deficient.⁶ This appears to be a critical factor that determines the proliferation and differentiation of T_H1 -related autoreactive cellular immune responses in these disorders. Systemic lupus erythematosus is associated with a T_H2 shift and an excessive production of IL-10, whereas IL-12 and TNF- α production appear to be deficient.

The effect of stress on the vulnerability to and the onset and progression of autoimmune disorders is extremely complex; often, stress is related to both triggering/exacerbation and amelioration of disease activity.^{2,6} Animal studies and certain clinical observations suggest that a hyperactive or hypoactive stress system may be associated with decreased or increased vulnerability to different types of autoimmune diseases. Thus, Fischer rats, which have a hyperactive stress system, are extremely resistant to the experimental induction of T_H1 -mediated autoimmune states, including arthritis, uveitis, and experimental allergic encephalomyelitis. Similarly, women in the third trimester of pregnancy, who have increased levels of cortisol, experience remission of T_H1 -type-mediated autoimmune diseases (such as rheumatoid arthritis, multiple sclerosis, type-1 diabetes mellitus, and autoimmune thyroid disease), possibly through the suppression of proinflammatory (IL-12 and TNF- α) and potentiation of anti-inflammatory (IL-4 and IL-10) cytokine production. Through a reciprocal mechanism, T_H2 -mediated autoimmune disorders that are mainly driven by IL-10 (such as systemic lupus erythematosus) may flare up in high cortisol and catecholamine output states (ie, during stress or pregnancy).

Conversely, Lewis rats, which possess a hypoactive HPA axis, are extremely prone to develop experimentally-induced T_H1 -mediated states (such as arthritis, uveitis, or experimental allergic encephalomyelitis). Similarly, clinical situations associated with decreased stress system activity are associated with increased expression or susceptibility to T_H1 -mediated autoimmune diseases (such as rheumatoid arthritis, multiple sclerosis, and autoimmune thyroid disease; Table III).² This includes the postpartum period and the period that follows the cure of endogenous Cushing's syndrome or the discontinuation of glucocorticoid therapy.^{2,14} This might also include the period that follows the cessation of chronic stress or a rebound effect on relief from stressors.

Epidemiologic studies suggest that severe stress, as reported by many patients, often precedes the development of certain T_H1 -mediated autoimmune states.⁶ Viral induction of autoimmunity is thought to occur by either bystander T-cell activation or molecular mimicry. Recent studies suggest that tissue-tropic Coxsackie B4 virus is associated with bystander damage and the development of type 1 diabetes mellitus, whereas human parvoviruses may be causative agents of rheumatoid arthritis. If future studies confirm these hypotheses, severe stress and severe suppression of cellular immunity may be a critical

factor that facilitates the establishment of pathogenic and tissue-tropic viral infection followed by "autoimmune" tissue damage. At a later stage, severe stress, by skewing the balance towards T_H2 , may ameliorate disease activity, whereas acute stress and peripheral release of immune CRH, through their proinflammatory effects, may in some cases exacerbate disease activity.

Allergic reactions such as asthma, eczema, hay fever, urticaria, and food allergy are characterized by dominant T_H2 responses, overproduction of histamine, and a shift to eosinophilia and immunoglobulin E production.⁴ As in the case of autoimmunity, the effects of stress on atopic reactions are complex; the effects occur at multiple levels and can be in either direction. Stress hormones that act at the level of APCs and lymphocytes may induce a T_H2 shift and facilitate or sustain atopic reactions; however, this can be antagonized by their effects on the mast cell (Fig 3).⁶ Glucocorticoids and catecholamines suppress the release of histamine by mast cells, thereby abolishing its proinflammatory, allergic, and bronchoconstrictor effects. Thus, reduced levels of epinephrine and cortisol and increased levels of IL-6 in the very early morning could contribute to nocturnal wheezing and have been linked to high circulating histamine levels in patients with asthma.

Several lines of evidence suggest that stress can increase the susceptibility to tumors, tumor growth, and metastases.⁶ The amount of IL-12 available at the tumor site appears to be critical for tumor regression. Thus, low levels of IL-12 have been associated with tumor growth, as opposed to tumor regression observed with the administration of IL-12 delivered *in situ* or systemically. On the other hand, local overproduction of IL-10 and TGF- β , by inhibiting the production of IL-12 and TNF- α and the cytotoxicity of NK and T-cytotoxic cells, seem to play an inappropriate immunosuppressive role, allowing increased malignant tumor growth. In humans, the augmentation of the rate of tumor progression and cancer-related death has been associated with stress, whereas treatment with cimetidine, an H_2 antagonist, correlated with increased survival in patients with gastric and colorectal cancer. These data suggest that stress hormone/histamine-induced suppression of cellular immunity may contribute to increased growth of certain tumors.

SYSTEMIC INFLAMMATION AND WELL-BEING

Like the stress response, the inflammatory reaction of an individual is crucial for survival of self and species.^{1,2} Also like the stress response, inflammation is meant to be tailored to the stimulus and be time limited. A fully fledged systemic inflammatory reaction consists of activation of immune and immune accessory cells and resultant stimulation of 2 major programs: (1) the sickness syndrome and (2) the classic stress syndrome. As a result, the acute phase reaction and the pain program, mediated by the afferent sensory and autonomic systems, are also activated (Table II; Fig 4).

Be it an inflammatory focus with spillover of inflammatory effector molecules into the systemic circulation or a truly generalized systemic inflammatory reaction, the programs that are activated during inflammation have both synergistic and antagonistic actions. For instance, the inflammatory cytokines stimulate C reactive protein production by the liver, and this effect is potentiated by glucocorticoids that also inhibit the secretion of inflammatory cytokines, bringing inflammation to a close.² Most of the manifestations of sickness syndrome (including anorexia/nausea, fatigue, and social withdrawal and/or depressed affect, somnolence, hyperalgesia with or without headache, fever, and an increased metabolic rate) are all suppressed by glucocorticoids. Yet, peripheral neuronal CRH, which is activated by stress and/or the inflammatory reaction, and substance P, which is activated by the inflammatory reaction itself, potentiate inflammation.^{1,2}

Chronic systemic inflammation, depending on its degree, varies from asymptomatic to severely symptomatic. Regardless of the presence of overt sickness syndrome manifestations, chronic elevations in circulating inflammatory cytokines and/or activation of the stress system result in a combination of immune and metabolic disturbances, which include endothelial inflammation and/or a T_H1 to T_H2 switch, osteoporosis, hypercoagulability, dyslipidemia, insulin resistance, carbohydrate intolerance and/or diabetes type 2, and hypertension.^{15,16} Many of these manifestations constitute the “visceral fat syndrome,” which deteriorates with time in patients with chronic inflammation and/or stress; this represents an exacerbation of a phenomenon that commonly occurs with advancing age in both men and women.¹¹ These chronic immune and metabolic changes all increase the number of deaths, primarily through cardiovascular-coronary heart and cerebrovascular disease—not only because of accelerated atherosclerosis but also because of cancer and infection. They also cause significant morbidity, including clinically significant osteoporosis.

Chronic or intermittent but frequent inflammation because of the presence of inflammatory foci (such as those of allergic rhinitis, bronchial asthma, periodontitis, *Helicobacter pylori* infection, or multiple sclerosis) may be responsible for the varying degrees and patterns of sickness syndrome manifestations in these patients, and may be associated with the chronic immune, metabolic, and cardiovascular complications of chronic inflammation and stress that was mentioned earlier. Although there are convincing epidemiologic studies of the relation between periodontitis and cardiovascular morbidity and mortality rates, there is scant evidence between allergic inflammation and such morbidity and mortality rates. A recent epidemiologic study reported a correlation between eosinophilia and cardiovascular deaths in a large number of subjects who were followed over 30 years.¹⁷ This relationship was independent of the body mass index of the subjects and suggested a doubling of the relative risk for cardiovascular death. No indices of chronic inflammation (such as C reactive protein or IL-6) were

measured. Another recent study demonstrated that elevated concentrations of immunoglobulin class E predicts a 2- to 8-fold risk for coronary heart disease independent of other risk factors such as age, smoking, and blood pressure.¹⁸ The eosinophilia and hyper-IgE globulinemia may be reflective of allergic inflammation and/or chronic stress.

Hypercytokinemia is not limited to conditions characterized by classic inflammatory stress (such as trauma and burns, infectious illnesses, autoimmune inflammatory diseases, and allergic inflammatory states; Table IV). Inflammatory phenomena in the CNS (eg, Alzheimer's disease, schizophrenia) and noninflammatory stresses are associated with peripheral elevations of IL-6 levels.

The chronic pain and fatigue syndromes

Several chronic pain and fatigue syndromes (such as fibromyalgia and chronic fatigue syndrome) have been associated with chronic sickness syndrome manifestations (such as fatigue and hyperalgesia) and with hypoactivity of the stress system (Table III).^{2,19} Interestingly, these clinical manifestations and the hypocortisolism of these patients are quite reminiscent of mild glucocorticoid deficiency (Addison's disease). Patients with glucocorticoid deficiency have elevated levels of proinflammatory cytokines such as IL-6, which may explain their typical sickness syndrome manifestations.^{11,20} When we administered human recombinant IL-6 to these patients, we induced an explosive sickness syndrome that was markedly more severe than that observed in healthy control subjects. In contrast, patients with endogenous hypercortisolism showed very little or no response to IL-6 (unpublished observation).⁵ It is tempting to speculate that patients with chronic pain and fatigue syndrome have an imbalance between the immune and inflammatory reactions and the stress response, which results in excessive sickness syndrome manifestations of the former versus the antithetical effects of the latter (Table II).

Obesity as a chronic inflammatory state

Adipose tissue secretes large amounts of TNF- α and IL-6 in a neurally, hormonally, and metabolically regulated fashion.²¹ The plasma levels of these cytokines are proportional to the body mass index and are further elevated in patients with visceral obesity.^{22,23} The secretion of inflammatory cytokines has a circadian pattern, with elevations in the evening and in the early morning hours.²⁴ This pattern is maintained in patients with inflammatory diseases and in obese patients, albeit at a higher level. This pattern is affected by the quality and quantity of sleep and correlates with manifestations of the sickness syndrome. In obesity, the hypercytokinemia is associated frequently with some manifestations of the sickness syndrome, such as fatigue and somnolence, and of the other pathways that may be activated during the inflammatory reaction, especially the acute phase reaction. Thus, obesity, especially the visceral type, can be considered as a chronic, smoldering inflammatory state, with many of the behavioral, immune, metabolic, and cardiovascular sequelae of such a state.

TABLE IV. States associated with hypercytokinemia

Trauma/burns
Infectious illnesses
Autoimmune inflammatory disease
Allergic inflammation
CNS inflammation
Noninflammatory stress
Obesity/visceral obesity
Aging

THERAPEUTIC PERSPECTIVES

Glucocorticoids and analogue agents that potentiate their actions are options for the treatment of autoimmune inflammatory diseases. By potentiating the secretion or the effects of hypothalamic CRH with CRH secretagogues, CRH agonists or CRH binding protein antagonists that cross the blood-brain barrier, the development of inflammatory disease in susceptible persons with a hypofunctional HPA axis may be prevented and, at the same time, correct CNS symptoms of CRH deficiency. Such an action could be envisioned for nonpeptidic substance P antagonists, which would be expected to reverse the CRH suppression that occurs in chronic inflammatory states, and act as a local anti-inflammatory agent.

Antagonists of proinflammatory peptides (such as substance P and CRH) may control inflammatory diseases or processes in which these peptides have a primary pathogenic role. Depending on their ability to cross the blood-brain barrier and the location of the therapeutic target, these antagonists could be used systemically or in a compartmentalized fashion. We recently used a nonpeptidic CRH receptor type-1 antagonist, antalarmin, in the treatment of rodent inflammation.^{25,26} Antalarmin suppressed acute neurogenic and chronic autoimmune inflammation in animals.

Once the mechanisms of acquired glucocorticoid resistance in rheumatoid arthritis, steroid-resistant asthma, systemic lupus erythematosus, and other inflammatory diseases are elucidated, therapy with the appropriate intracellular agents that will sensitize the cascade of glucocorticoid action in immune cells, treatment with cytokines or their antagonists, or pharmacologic agents that influence their secretion and action may become available for the management of these disorders.

Moreover, blocking the effect of stress by β -adrenoreceptor and/or H_2 -receptor antagonists may result in increases in T_H1 responses that may be useful in the management of certain infections or tumors, whereas the combined administration of β -adrenoreceptor agonists and glucocorticoids may help in the management of certain T_H1 -mediated autoimmune diseases. Finally, CRH antagonists (such as antalarmin) may help prevent stress-induced T_H1 suppression and the triggering of stress-induced allergic or vasokinetic phenomena.^{25,26}

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