CLINICAL MICROBIOLOGY REVIEWS, Apr. 1994, p. 200–212
0893-8512/94/$04.00+0

Vol. 7, No. 2

Psychoneuroimmunology: Stress Effects on Pathogenesis and Immunity during Infection

JOHN F. SHERIDAN,[1,2]* CATHLEEN DOBBS,[2] DAVID BROWN,[3] AND BRUCE ZWILLING[3]

Section of Oral Biology,[1] Department of Medical Microbiology and Immunology,[2] and Department of Microbiology,[3] Colleges of Dentistry, Medicine, and Biological Sciences, The Ohio State University, Columbus, Ohio 43210

INTRODUCTION

Psychoneuroimmunology is an interdisciplinary field concerned with the study of behavior-neuroendocrine-immune interactions and their potential health consequences (2). This review focuses on the effects of stressors, and neuroendocrine responses to stressors, on the pathogenesis of, and immune response to, infectious disease.

Stress and Immunomodulation

In general, a stressor can be defined as any external or internal challenge that disrupts the internal environment. The mammalian response to a stressor involves a variety of adaptive physiologic mechanisms designed to restore homeostasis (131). Physiologic responses to stressors are mediated primarily by two neuroendocrine systems: the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. Elevations of tissue and plasma catecholamines result from increased SNS activity induced by a variety of stressors. SNS activation results in the local release of norepinephrine from sympathetic nerve terminals and in the hormonal secretion of epinephrine from chromaffin cells of the adrenal medulla. Through interactions with α- and β-adrenergic receptors, norepinephrine and epinephrine mediate adaptive cardiovascular and metabolic effects under conditions of stress. There is considerable evidence to indicate that the SNS can also modulate immune responses. For example, chemical sympathectomy has been shown to alter immune responses. Treatment of animals with 6-hydroxydopamine, a toxin that destroys noradrenergic neurons, has been found to reduce the primary antibody response to T-dependent antigens (73, 108) and to suppress alloantigen-induced cytotoxic T-lymphocyte (CTL) activity (109). In addition, it has been demonstrated that both primary and secondary lymphoid organs are directly innervated by noradrenergic postganglionic sympathetic neurons (44). The distribution of nerve fibers in these organs suggests that immune effector cells contained within them are direct targets of this innervation (45).

Support for direct effects of catecholamines on immunoreactivity comes from the demonstration of adrenergic receptors on immune cells. β-Adrenergic receptors are expressed on T and B lymphocytes, macrophages, neutrophils, and natural killer (NK) cells (1, 53, 55, 105, 110, 122). Cells possessing these receptors would be expected to respond (depending on their state of activation) to neuronal norepinephrine and adrenal medullary epinephrine released during the SNS response to a stressor. The ability of mononuclear cells to respond to β-adrenergic receptor stimulation by elevating intracellular cyclic AMP has been suggested to be the primary mechanism by which catecholamines regulate immune responses (111). In vitro and in vivo studies have shown that catecholamines alter a variety of immune responses. Modulatory effects of catecholamines on lymphocyte migration and proliferation, antibody secretion, cytotoxic activity, and macrophage activation have been demonstrated (102, 120, 151). In addition, norepinephrine has been shown to inhibit cytokine-induced, major histocompatibility complex (MHC) class II antigen expression on antigen-presenting cells (52).

Stressful stimuli also activate the HPA axis, leading, ultimately, to increases in plasma glucocorticoids (GC). Under conditions of stress, GC mediate adaptive metabolic, cardiovascular, and anti-inflammatory effects. GC actions are initiated through intracellular GC receptors. The production and secretion of GC by cells of the zona fasciculata of the adrenal cortex is stimulated by pituitary adrenocorticotropic hormone (ACTH) (5). Stress-induced ACTH production is elicited primarily by hypothalamic corticotropin-releasing factor (CRF) (135, 155). In addition to ACTH, CRF also stimulates the secretion of other peptides derived from expression of the proopiomelanocortin gene (41, 112), including the opioid peptides β-endorphin and methionine-enkephalin. Although their precise roles in stress-induced physiologic responses are not yet fully understood, the opioid peptides have been implicated in learning and pain control responses (103).

The ability of GC hormones to modulate immune responses has been widely studied (123). Mononuclear cells possess receptors for GC (32, 160), and direct suppressive effects of GC on immune effector cells have been demonstrated. GC inhibit interleukin 2 (IL-2) gene expression by lymphocytes at the transcriptional level and IL-1 gene expression by macrophages at both transcriptional and posttranscriptional levels (94, 106, 107, 124, 154). In addition, they have been shown to inhibit MHC class II antigen expression, tumor necrosis factor

* Corresponding author. Mailing address: Box 192, Postle Hall, 305 W. 12th Ave., Ohio State University, Columbus, OH 43210. Phone: (614) 292-2012. Fax: (614) 292-7619.

TABLE 1. Summary of stress, the immune response, and microbial pathogenesis in animals

Pathogen	Animal	Stressor	Finding(s)[a]	Reference(s)
Type I streptococci	Mouse	Adrenocortical extract	↑ Survival time	157
Plasmodium berghei	Mouse	GC	↓ Parasitemia, ↓ reticulocyte counts, ↑ survival time	146
	Rat	GC	↑ Survival time, ↑ mortality	86
	Mouse	Electric shock	↑ Survival time	50
	Mouse	Novel environment	No effect	50
Yersinia (*Pasteurella*) *pestis*	Mouse	GC	Invasive infection, bacteremia, death	126
Trichinella spiralis	Mouse	GC	↓ Nematode clearance, lymphocytopenia, eosinopenia, ↓ cellular infiltration	28, 29
Mycobacterium tuberculosis	Mouse	GC	↓ Cellular infiltration, ↑ bacterial multiplication, disseminated infection, death	136
Salmonella typhimurium	Mouse	Crowding	↑ Susceptibility, ↓ antibody response	39
Hymenolepis nana	Mouse	Predator exposure	↑ Reinfection rate	74
Escherichia coli	Chicken	Cold	↑ Resistance	69
	Chicken	Social stress	↑ Resistance	68
Mycobacterium avium	Mouse	Restraint	↑ Susceptibility	18
	Chicken	Social stress	↑ Granuloma formation	72
Salmonella enteritidis	Chicken	Fasting	↑ Susceptibility to infection, ↑ severity of infection	77, 78

[a] ↑, increase; ↓, decrease.

production by macrophages (10, 148, 164), and gamma interferon (IFN-γ) synthesis. Intercellular adhesion molecule-1 and IL-2 receptor expression are also inhibited by GC (64, 139). GC also exert potent anti-inflammatory effects by inhibiting phospholipase A_2 activity (11) and have been shown to alter lymphocyte trafficking (25, 43). Furthermore, GC have been shown to inhibit T-cell binding to endothelial cells by modulating expression of adhesion molecules on these cells (40).

Recently, the immunomodulatory capabilities of other products of the HPA axis have been recognized. Functional receptors for CRF have been demonstrated on macrophages (158, 159). CRF has also been shown to alter NK cell activity (20, 83, 84), but this effect is thought to be centrally mediated and not due to a direct effect of CRF on NK cells (82).

There is evidence, however, for direct effects of ACTH on several different types of immune cells, and ACTH receptors have been demonstrated on mononuclear cells (15, 88, 147). ACTH has been shown to inhibit antibody production (89) and to enhance proliferation by B lymphocytes (17). ACTH has also been shown to inhibit T-lymphocyte IFN-γ production (90) and IFN-γ-induced macrophage activation (102) and MHC class II expression (164).

The potential immunomodulatory effects of the opioid peptides have also been recently recognized. Opioid binding sites have been demonstrated on lymphocytes, polymorphonuclear leukocytes, and platelets (4, 119). β-Endorphin and methionine-enkephalin have been shown to enhance the generation of CTLs (21) and NK cell cytotoxicity (42, 114) in vitro. However, the in vivo stress-induced release of opioid peptides has been found to enhance (82) or depress (142) NK activity, depending on the nature of the stressor. In addition, opioid peptides have been shown to enhance IL-2 production by lymphocytes (58) and IFN-γ production by lymphocytes and NK cells (19, 113). Opioid peptides have been reported to enhance (56, 57) or depress (56, 115, 116) mitogen-induced lymphocyte proliferation.

The above discussion has focused on the ability of neurotransmitters and hormones, released from the neuroendocrine system in response to stressors, to affect the function of cells of the immune system. Immune function is known to be an important mediator of infectious disease susceptibility and outcomes. The remainder of this review highlights studies examining the effects of stressors on the pathogenesis of, and immune responses to, infectious diseases.

STRESS AND MICROBIAL INFECTIONS

Perhaps the first observation that a stressful event could alter host-parasite relationships was reported by Ishigami (85), who found that the incidence of tuberculosis correlated with a decrease in opsonic index of sera obtained from Japanese school children. The increase in tuberculosis in school children as well as in their instructors was attributed to the stressful environment found in the schools. Indeed, these observations may have been the foundation for the generally held belief that some stressful conditions serve as a cofactor in the development of active tuberculosis infections (30, 161). However, despite this conventional wisdom, little or no experimental evidence is available that shows that stress affects the outcome of the relationship of a host with microbial pathogens (Table 1).

Early studies that indicated that the HPA axis may be important in the modulation of infectious disease outcomes were limited to assessing the effects of exogenously injected adrenal cortical extract or cortisol. These studies showed that adrenal cortical preparations increased the susceptibility of experimental animals (primarily mice and rats) to pneumococcal infection (157) and to growth of *Plasmodium berghei* (86, 146), *Yersinia* (*Pasteurella*) *pestis* (126), *Trichinella spiralis* (28, 29), and mycobacteria (136). All of these studies concluded that treatment of animals with adrenal cortical preparations increased their susceptibility to microbial growth.

Several different stress paradigms have also been shown to adversely affect the survival of infected animals. Thus, Friedman et al. (50) showed that crowding stress altered the resistance of mice to malaria infection. In another study, crowding stress was shown to result in a marked increase in the susceptibility of mice to *Salmonella typhimurium* (39). Hamilton reported that predator stress (cat) reduced the resistance of immune mice to reinfection by the cestode *Hymenolepis nana* (74), and cold stress was shown to inhibit the clearance of *Staphylococcus albus* and *Proteus mirabilis* from the lungs of mice (66).

Studies of the effects of stress on the resistance of farm

animals to experimental infection has also been assessed. In a series of recent studies, Gross and coworkers showed that social stress increased the susceptibility of chickens to aerosol challenge with *Escherichia coli* or to challenge with *Mycobacterium avium* (68, 69, 72). Holt and Porter found that food deprivation increased the susceptibility of chickens to *Salmonella enteritidis* infection and resulted in a more severe infection (77, 78). Zamri-Saad et al. (163) found that transport stress was associated with an increased susceptibility of goats to infection with *Pasteurella haemolytica*. In this case, transport served as a cofactor to previous injection with dexamethasone. Animals injected with dexamethasone alone did not become infected with the pasteurellae.

Stress and Mycobacterial Disease

The incidence of mycobacterial disease has increased significantly during the past 10 years. While much of the increase in tuberculosis and of infection by the *M. avium* complex has been observed in patients infected with human immunodeficiency virus (HIV), the incidence of tuberculosis has increased in this country in individuals not infected with HIV and continues to be a significant public health problem worldwide (30, 101, 129).

Generally, most healthy individuals who are infected with *M. tuberculosis* develop delayed hypersensitivity and a protective immune response that controls the growth of the microorganism (34). During the initial stages of the disease, the bacilli grow within alveolar macrophages that are eventually killed by bacteria. Within 2 to 3 weeks of infection, delayed hypersensitivity responses develop which result in the destruction of infected macrophages, the formation of caseous necrosis, and the creation of an environment that will not support mycobacterial growth. The cell-mediated immune response prevents further multiplication of bacilli. The extent to which the growth of the microorganism is controlled may vary within different necrotic lesions. In most infected individuals, the disease may remain dormant until the cell-mediated immune response is compromised. Thus, the reactivation of disease has been attributed to any one of several factors that compromise the cell-mediated immune response. Included among these are HIV infection, immunosuppressive cancer chemotherapy, immunosenescence that accompanies aging, chronic alcoholism with associated protein malnutrition, and stress.

Injection of mice with mycobacteria results in two phenotypic patterns of growth. Following intravenous injection, mycobacteria grow exponentially in some strains of mice but not in others. On the basis of different growth patterns, strains of mice can be classified as resistant or susceptible to mycobacterial growth (49, 67). The gene that controls resistance to mycobacterial growth in mice, termed *Bcg*, maps to a gene on chromosome 1 (130). A group of genes that are linked to *Bcg* in mice form a syntenic group of genes on human chromosome 2q (141). Studies by Johnson and Zwilling (91), as well as by Denis et al. (35, 36), have indicated that the differences in the growth patterns of the mycobacteria are due to differences in macrophage activation. Thus, mature tissue macrophages from BCG-resistant (Bcg^r) mice can control the growth of the mycobacteria, whereas macrophages from BCG-susceptible (Bcg^s) mice cannot.

Given the differences in the ability of macrophages from congenic BCG-resistant and -susceptible mice to control mycobacterial growth, and the possibility that stress may alter the interaction between the host and the parasite, we have extended our studies to include an assessment of the role of HPA axis activation and mycobacterial growth. The design of these studies was based on previous observations that restraint stress

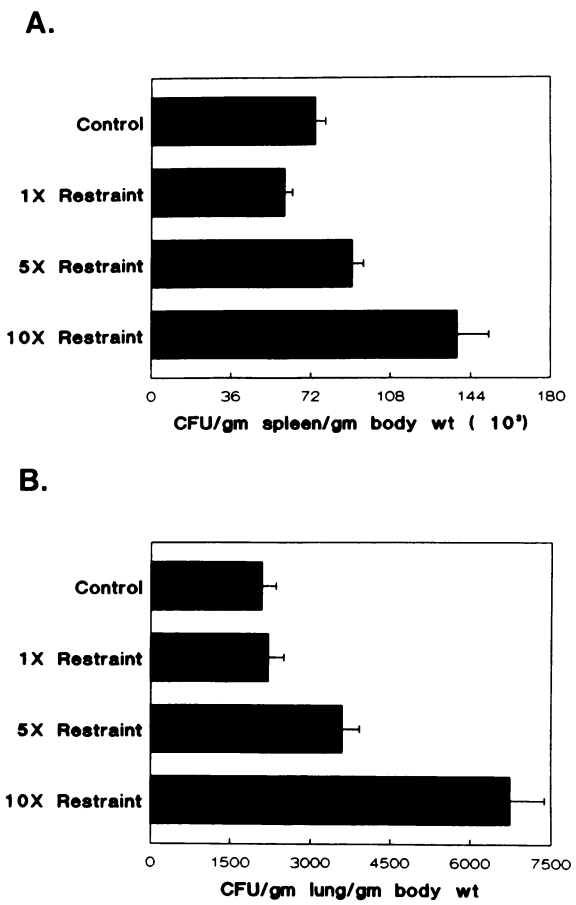

FIG. 1. Effect of restraint stress on mycobacterial growth in mice. BALB/c mice were injected with 5×10^4 CFU of *M. avium* intravenously. After a period of 4 h to allow for dissemination of the microorganisms, the mice were stressed by restraint for 1, 5, or 10 cycles (18 h per cycle). The number of CFU of mycobacteria was determined 12 days after injection in the spleens (A) and lungs (B) by plate count, using Middlebrook 7H11 agar. The number of CFU was adjusted to reflect differences in organ weight and body weight. The numbers of CFU isolated from the spleens and lungs prior to restraint were 13,519 CFU/g of spleen per g of body weight and 584 CFU/g of lung per g of body weight. The data are the means ± standard deviations for seven animals per group. The differences between 5- and 10-cycle restraint and control mice were significant by analysis of variance ($P < 0.001$). Reprinted from reference 18 with permission of the publisher.

suppressed MHC class II expression by macrophages from Bcg^s mice but did not affect the expression of MHC class II expression by macrophages from Bcg^r mice (164, 165). We found that the timing of the stressor was an important factor in suppressing macrophage function and that the effect of stress was ameliorated by the intensity of the immunological stimulus (164). In order to assess the effect of stress on mycobacterial growth, studies by Brown et al. (18) have used a restraint stress paradigm. Thus, mice were stressed by restraint immediately following the intravenous injection of 5×10^4 CFU of *M. avium*. Mice were stressed by restraint for 1, 5, or 10 cycles (18 h per cycle). Each cycle was followed by a 6-h rest period. The animals were sacrificed 12 days after the injection of mycobacteria, and the numbers of mycobacteria present in the spleens and lungs were determined by serial dilution and plate count, using Middlebrook 7H9 agar. The results in Fig. 1 show that

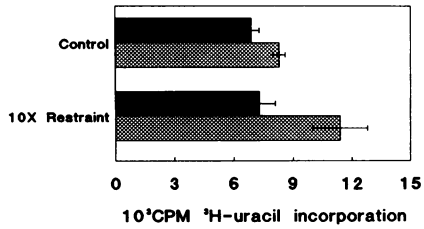

FIG. 2. Effect of restraint stress on antimycobacterial activity of macrophages from BALB/c.*Bcg*^{r} (■) and BALB/c.*Bcg*^{s} (▩) mice. Splenic macrophages were isolated from mice and infected with *M. avium*. The growth of the mycobacteria was determined by pulsing cultures with [^{3}H]uracil after lysis of the macrophages with saponin. Infected cultures were pulsed immediately following a period of phagocytosis to determine the numbers of microorganisms taken up initially. Replicate cultures were pulsed after 5 days of growth within macrophages. The amount of [^{3}H]uracil taken up by the *M. avium* cells following release from the *Bcg*^{s} macrophages immediately after phagocytosis was 574 cpm, while that taken up by *M. avium* cells following release from *Bcg*^{r} macrophages was 523 cpm and did not differ as a result of restraint of the mice. The *M. avium* cells released from macrophages immediately after phagocytosis incorporated 45,334 cpm of [^{3}H]uracil when pulsed after 5 days of growth, and this amount of label did not differ between bacteria released from macrophages from *Bcg*^{r} and *Bcg*^{s} mice. The data are the counts per minute of [^{3}H]uracil taken up by the bacteria released from macrophages after 5 days of in vitro culture. The data are from a representative experiment. Reprinted from reference 18 with permission of the publisher.

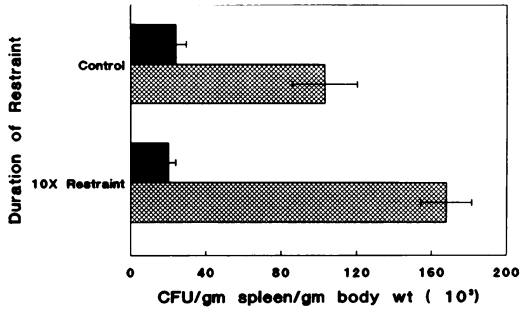

FIG. 3. Differential effect of restraint stress on BALB/c.*Bcg*^{r} (■) and BALB/c.*Bcg*^{s} (▩) mice. Mice were injected with *M. avium* and stressed by restraint for 10 cycles, as described in the legend to Fig. 1. The numbers of CFU in the spleens were determined 12 days after infection. The numbers of CFU isolated from the spleens of *Bcg*^{r} and *Bcg*^{s} mice prior to restraint were 19,462 and 18,083 CFU/g of spleen per g of body weight, respectively. The data are the means ± standard deviations for seven animals per group. The difference between the values for the restraint and control groups of *Bcg*^{s} mice was significant ($P < 0.001$). The difference between the growth of mycobacteria in the spleens of *Bcg*^{r} mice versus growth in *Bcg*^{s} mice was also significant ($P < 0.001$). Reprinted from reference 18 with permission of the publisher.

the numbers of mycobacteria found in the spleens (panel A) and lungs (panel B) of mice that were stressed for a single 18-h period were similar to those found in the spleens of unstressed mice. In contrast, multiple stress experiences increased the susceptibility of mice to mycobacterial growth (18).

The differences in the effect of multiple cycles of restraint were also apparent when we tested the ability of splenic macrophages to support the growth of mycobacteria (Fig. 2). Thus, the macrophages from *Bcg*^{s} mice restrained for multiple cycles were more permissive for mycobacterial growth than macrophages from nonrestrained control mice (macrophages from *Bcg*^{r} mice did not show the same effect of restraint).

When we compared the effect of stress on the growth of mycobacteria in congenic BCG-resistant or -susceptible mice, we found that stress did not alter the growth of the mycobacteria in the resistant mice but increased the susceptibility of the susceptible mice (Fig. 3).

The differences we have observed in the effect of stress on the growth of mycobacteria in vivo may have important implications in the human population. Several reports have indicated that humans, like mice, differ in susceptibility to mycobacterial diseases. Recent epidemiological studies have indicated that blacks may be more susceptible than whites to infection with *M. tuberculosis* and that macrophages from blacks are more permissive to the growth of *M. tuberculosis* (33, 150). If we extrapolate our observations on the effect of an experimental stressor on mycobacterial resistance in the mouse model to the human population, then it is possible that susceptible human populations may also be more easily affected by stress than the resistant populations, leading to reactivation of disease.

Stress and Viral Infections in Humans

Table 2 summarizes the results of studies of the effects of stress on viral infections in humans. Stress has long been identified as a cofactor in the reactivation of latent virus in humans (93). The periodic reactivation of herpes simplex virus (HSV) from the latent state frequently leads to the development of recurrent infection in HSV-seropositive individuals. HSV, which resides in the peripheral ganglia of latently infected individuals, is carried back by axonal transport to cells innervated by infected neurons (38). A number of stimuli, both local and systemic, have been associated with reactivation of HSV in latently infected neurons. Among the systemic stimuli associated with recurrent disease are physical and emotional stress, hormonal changes, fever, and immune suppression (31, 137, 140).

Recent studies have demonstrated an association between emotional stress and higher rates and longer duration of recurrent genital HSV infections (62, 145, 156). These studies suggest a linkage between stress and HSV recurrent disease. However, because of the retrospective nature of these studies and the failure of recent prospective studies to demonstrate significant relationships between stress and the onset of recurrent genital herpes episodes (93, 132), it is difficult to argue for causality. Furthermore, the lack of immunologic and virologic assessment in these studies, with the exception of the study by Kemeny et al. (93), obscures an examination of the mechanisms that underlie the relationship between stress and the reactivation of latent viral infection.

Several studies, however, have explored the relationship between stressful life experiences and the immunologic control of latent viral infection. Lower cellular immune control of herpesvirus latency corresponds to higher antibody titers to herpesvirus in serum (59). Both acute (examination stress and marital discord) and chronic (living near site of a nuclear disaster and caring for a relative with Alzheimer's disease) stressors have been associated with elevated serum antibody titers to latent herpesviruses (Epstein-Barr virus, HSV type 1, and cytomegalovirus) (61, 96, 97, 99, 100, 117). This evidence suggests that factors controlling the antiviral cellular immune response may mediate the relationship between stress and the reactivation of latent virus.

Although it has been suggested that stress increases susceptibility to infections of the upper respiratory tract, only a few studies have provided direct evidence that stress increases the

TABLE 2. Summary of stress, viral pathogenesis, and antiviral immunity in humans[a]

Virus	Subjects	Design	Stressor(s)	Finding(s)[b]	Reference(s)
HSV	Genital herpes patients	Retrospective	Psychiatric illness	↑ Recurrences	62
		Retrospective	Life events	↑ Duration	145
		Retrospective	Life events, social support	↑ Recurrences	156
		Prospective	Life events, mood	↑ Recurrences	93
		Prospective	Daily stress	No effect	132
	Residents of TMI	Concurrent	Stress of living near TMI	↑ Antibody to HSV-1	117
	Separated/divorced men	Concurrent	Marital discord	↑ Antibody to HSV-1	97
Epstein-Barr	Medical students	Prospective	Exams	↑ Antibody to EBV	61
	Caregivers of AD victims	Concurrent	Caregiving	↑ Antibody to EBV	96, 99
	Separated/divorced men	Concurrent	Marital discord	↑ Antibody to EBV	97
Cytomegalovirus	Residents of TMI	Concurrent	Stress of living near TMI	↑ Antibody to CMV	117
Influenza	Volunteers	Prospective	Personality, life events	↑ Nasal secretion	16
	Family members	Prospective	Family dysfunction	↑ Frequency of infection	26
Rhinovirus	Volunteers	Prospective	Personality, life events	↑ Nasal secretion, virus shed	16
		Prospective	Personality, life events	↑ Frequency of infection	27
Respiratory syncytial	Volunteers	Prospective	Personality, life events	↑ Frequency of infection	27
Coronavirus	Volunteers	Prospective	Personality, life events	↑ Frequency of infection	27
HIV-1	Male homosexuals	Prospective	Serostatus notification	No effect	81
	Seropositive male homosexuals	Retrospective	Life events	↓ Total lymphocyte count	63
		Retrospective	Life events	No effect	95
	Seropositive adults	Prospective	Life events, mood	No effect	127
		Prospective	Social support	No effect	149
Hepatitis B	Medical students	Prospective	Life events	↑ Antibody response to vaccine	128
		Prospective	Exams, social support	↓ & delayed antibody response to vaccine, ↓ T-cell response	60

[a] TMI, Three Mile Island; AD, Alzheimer's disease; EBV, Epstein-Barr virus; CMV, cytomegalovirus.
[b] ↑, increase; ↓, decrease.

frequency of naturally acquired, clinically documented, viral respiratory illness (26, 65). These studies, however, did not control for the effects of health or behavioral practices on viral exposure. Studies by Broadbent et al. (16) and Cohen et al. (27) addressed the deficiencies of the other studies by experimentally exposing volunteers to cold viruses. In the Broadbent study, stress was associated with increased nasal secretions following inoculation with rhinovirus or influenza A virus. In the Cohen study, stress was associated with an increased infection rate following rhinovirus, respiratory syncytial virus, or coronavirus challenge but was not associated with an increased incidence of clinical colds. Although studies showed a relationship between stress and colds, neither study examined the mediating mechanisms. Both stress-induced changes in immunity (27, 152) and the nasal mucosa (23) have been suggested as possible causes.

The possibility that stress may influence the course of HIV-1 infection by altering immune function has been suggested (75, 98). Recent studies have explored this possibility (63, 81, 95, 127, 149), but only the study by Goodkin et al. (63) has found an association between stress and immune measures in HIV-1 infection. In this retrospective study of 11 asymptomatic seropositive homosexual males, high levels of stress and a low ability to cope with stress were associated with lower total lymphocyte counts. High ability to cope with stress was associated with greater numbers of $CD4^+$ T lymphocytes in the peripheral blood. These results should be interpreted in light of the small sample size used in the study.

The effect of stress on the response to vaccination has also been examined. Two studies have investigated the relationships between stress and the antibody response to a recombinant hepatitis B vaccine. Petry et al. (128) studied the effects of stress on the peak antibody response to recombinant hepatitis B vaccination in 81 medical students. Higher levels of stress and anxiety during the 6-month period following the first dose of hepatitis B vaccine were associated with higher peak anti-

TABLE 3. Summary of animal models of stress and viral pathogenesis

Virus	Animal	Stressor	Finding(s)[a]	Reference
Coronavirus	Pig	Cold	↑ Gastroenteritis	144
Newcastle disease	Chicken	Social stress	↑ Viral dissemination, virus titer	121
Bovine herpesvirus	Calf	Transportation	↑ Pneumonia, mortality	48
	Heifer	Transportation	Viral reactivation	153
Coxsackievirus B	Mouse	Avoidance learning	↑ Weight loss, mortality, virus titer	92
	Mouse	Forced exercise	↑ Myocarditis, mortality, virus titer	54
	Mouse	Forced exercise	↑ Inflammation, necrosis	79
Encephalomyocarditis	Mouse	Isolation	↑ Mortality	51
HSV	Mouse	Avoidance learning	↑ Mortality	133
	Mouse	Restraint	↑ Virus titer	12
	Mouse	Foot shock	↑ Virus titer	104
Poliomyelitis	Mouse	Forced exercise	↑ Paralysis, mortality	138
Vesicular stomatitis	Mouse	Sound	↑ Mortality	7
	Mouse	Avoidance learning	↓ Viral clearance	162
Influenza A	Mouse	Immobilization	↑ Viral dissemination, mortality	24
	Mouse	Forced exercise	↑/↓ Mortality	80
	Mouse	Restraint	↓ Inflammation	143
	Mouse	Restraint	↓ Mortality, inflammation	76
West Nile	Mouse	Cold	↑ Mortality; accelerated mortality, symptom onset	7
	Mouse	Isolation	↑ Mortality	7
Langat	Mouse	Immobilization	↑ Viral replication, encephalitis, mortality	125
Sindbis	Mouse	Cold	Encephalitis	8
	Mouse	Isolation	Encephalitis	8
West Nile, attenuated, noninvasive	Mouse	Cold	Encephalitis	9
	Mouse	Isolation	Encephalitis	9
Keystone	Rat	GC	↑ Susceptibility	118
Adenovirus	Chicken	Fasting	↑ Splenomegaly	71
	Chicken	Neglect	↑ Splenomegaly	71
	Chicken	GC	↑ Splenomegaly	71
	Turkey	Social stress	↑ Hemorrhagic enteritis	70

[a] ↑, increase; ↓, decrease.

body titers. Glaser et al. (60) studied the effects of examination stress on the development of the antibody response to hepatitis B vaccine in 48 seronegative medical students. All subjects received a series of three hepatitis B vaccine doses according to the same standard immunization protocol used by Petry et al. (128). However, each dose was administered on the third day of a 3-day examination series. Twelve subjects seroconverted for hepatitis B surface antigen between the first and second vaccine doses. These "early" seroconvertors were significantly less anxious and less stressed than "late" seroconvertors. However, the antibody titers to hepatitis B surface antigen achieved by the third dose did not differ between early and late seroconvertors. Overall, this study demonstrated that stress appeared to delay the humoral immune response to hepatitis B vaccination.

EXPERIMENTAL ANIMAL MODELS OF STRESS AND VIRAL INFECTION

Experimental animal models have also been used to study the effects of stress on viral infection (Tables 3 and 4). As with microbial infections, some of these studies have assessed the effects of stressors on the resistance of farm animals to viral infection (3, 48, 121, 144, 153). Shimuzu et al. (144) found that

TABLE 4. Summary of animal models of stress and antiviral immunity

Virus	Animal	Stressor	Finding(s)[a]	Reference
Vesicular stomatitis	Mouse	Sound	↓ IFN, no effect neutralizing antibody	22
	Mouse	Avoidance learning	No effect neutralizing antibody	162
Coxsackievirus B	Mouse	Forced exercise	↓ Neutralizing antibody	134
Influenza A	Mouse	Immobilization	↓ IFN-α	24
	Mouse	Restraint	↓ Cellular infiltration, IL-2	143
	Mouse	Restraint	Delayed antibody response, ↓ IL-2	46
	Mouse	Restraint	↓ Lymphadenopathy, cellular infiltration, IL-2	76
Newcastle disease	Chicken	Heat	↑/↓ Antibody response	6
Keystone	Rat	GC	↓ Neutralizing antibody	118
HSV	Mouse	Restraint	↓ Lymphadenopathy, CTL & NK activity	12
	Mouse	Foot shock	↓ Lymphadenopathy, CTL activity & antibody response	104
	Mouse	Restraint	↓ Memory CTL activity	13

[a] ↑, increase; ↓, decrease.

exposure of pigs to low ambient temperature (4°C) increased their susceptibility to transmissible gastroenteritis virus infection. Mohamed and Hansen (121) demonstrated that social stress increased the susceptibility of chickens to Newcastle disease virus infection. In cattle, transport stress increased pneumonia and mortality following aerosol challenge with bovine herpesvirus-1 (48) and led to reactivation of latent bovine herpesvirus-1 infection (153).

Most studies, however, have examined the effects of stressors on the resistance of rodents to viral infection. Early studies demonstrated that a variety of stressors increased the susceptibility of mice to coxsackievirus B3 (54, 92), encephalomyocarditis virus (51), HSV (133), poliomyelitis virus (138), and vesicular stomatitis virus (87, 162) infection. In more recent studies, forced exercise (80) and immobilization stress (24) have been reported to decrease the resistance of mice to influenza A virus infection; cold and isolation stress have been shown to increase the susceptibility of mice to West Nile virus encephalitis (7).

Other recent studies in rodents have examined the ability of stressors to modulate the neuroinvasiveness of nonneurovirulent virus strains. Ozherelkov et al. (125) found that mice subjected to immobilization stress developed encephalitis following an experimental Langat virus infection while nonstressed mice remained asymptomatic. Ben-Nathan et al. found that both cold and isolation stress induced the neuroinvasiveness of Sindbis virus (8) as well as of an attenuated, noninvasive strain of West Nile virus (9).

The effects of various stressors on the immune responses to experimental viral infections have also been assessed. An early study showed that, in addition to increasing the susceptibility of mice to vesicular stomatitis virus infection, noise stress suppressed interferon production but did not alter the neutralizing antibody response to vesicular stomatitis virus (22). More recently, in other murine models, forced exercise significantly reduced the titer of neutralizing antibody to coxsackievirus B3 (134) and increased the number of $T_{cytotoxic}/T_{suppressor}$ cells in myocardial lesions (79). In addition, immobilization suppressed IFN-α production in response to influenza A virus infection (24). In chickens, exposure to heat stress significantly lowered the antibody response to Newcastle disease virus (6).

The roles of GC in the stress-induced alteration of viral pathogenesis and antiviral immunity have been assessed by a variety of methods. Nonstressed animals have been treated with high levels of exogenous GC to simulate a stress-induced response. Treatment of cotton rats with prednisolone, a potent synthetic GC, significantly increased their susceptibility to Keystone virus infection (118). In addition, the neutralizing antibody response to Keystone virus was delayed and depressed in magnitude in GC-treated rats. Gross and Domermuth (71) found that corticosterone administration increased the susceptibility of chickens to challenge with avian adenovirus type II. Stressed animals have been adrenalectomized or treated with GC antagonists to block stress-induced elevations of plasma GC. Adrenalectomy did not abrogate the stress-induced increase in the susceptibility of mice to vesicular stomatitis virus (87, 162). Administration of metyrapone, a GC synthesis inhibitor, eliminated the increased susceptibility to avian adenovirus in turkeys and to Newcastle disease virus in chickens subjected to social stress (70).

The studies cited above indicate that animal models of infectious disease have provided investigators with the tools to explore the mechanisms of neuroendocrine-immune interactions that affect microbial pathogenesis. A variety of experimental viral infections in rodents have been used to provide fundamental insight into the kinetics and pattern of virus

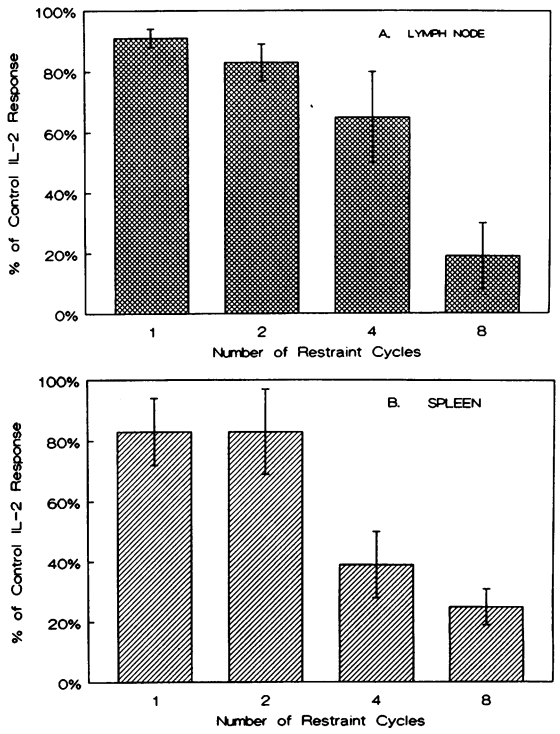

FIG. 4. Number of restraint cycles needed to suppress IL-2 response to influenza A/PR8 virus. Mice were restrained prior to infection and then for two, four, or eight cycles following infection. At 14 days postinfection, the IL-2 response of cells from the mediastinal lymph nodes (A) or spleens (B) was measured in vitro. Data are presented as percentage of control (nonrestrained/infected) IL-2 response for six to nine animals per group (mean ± standard error of the mean). Reprinted from reference 143 with permission of the publisher.

replication, the induction and expression of the infected host's immune response, and the pathophysiology of the infectious disease process. Similarly, rodents have been used extensively in the characterization of neuroendocrine responses to stressors. The thrust of our research over the past 5 years has involved the use of well-characterized animal models of HSV and influenza virus infections to explore the nature of neuroendocrine-immune interactions in the setting of an experimental stressor. We have chosen to use repetitive cycles of restraint as a stressor and measurements of plasma corticosterone and tissue catecholamines as indicators of activation of the HPA axis and the SNS, respectively. In this setting, we have been able to examine cellular and humoral immune responses to viral infection and explore the effects of a stressor on the pathophysiology of an infectious disease process.

In our early studies, parametric variations of the stressor (restraint) were tested for effects on the cellular immune response and the pathophysiology of an influenza virus infection. We determined that although short cycles of restraint (<6 h) elevated plasma GC levels, they had no effect on the IL-2 response to influenza virus, nor did they alter the pathophysiology of the infectious process (46). Similarly, a low number (<4 cycles) of longer cycles of restraint (>12 h) did not affect these parameters. However, when the number of restraint cycles was ≥4 (16 h per cycle), the IL-2 response was significantly depressed (Fig. 4) and mononuclear cell infiltration into the lung was diminished (143). Once we had established that repetitive cycles of physical restraint could depress a T-cell

response during infection, we used both models of acute viral infection (influenza virus and HSV) to explore stress-induced modulation of antiviral immunity and the effects of stress on viral pathogenesis.

To examine the effects of physical restraint on a viral infection in the respiratory tract, C57BL/6 male mice were infected intranasally with 32 hemagglutinating units of influenza A/PR8 virus, and restraint (16 h per cycle) was started 2 days prior to infection and continued throughout the infection period. Mice deprived of food and water, but not restrained, served as a control group, and a nontreated home cage group was also included. Physical restraint significantly altered the inflammatory response during infection; a pattern of reduced mononuclear cellular infiltration and less lung consolidation coincided with elevated plasma corticosterone levels. Virus-specific T-cell cytokine responses (IL-2) by lymph node and splenic lymphocytes were also significantly depressed in restraint-stressed animals (143). The depressed IL-2 response to influenza virus was not due to a diminished frequency of virus-specific, cytokine-secreting T cells because limiting-dilution analysis indicated similar frequencies in restrained and control mice. However, the reduced cell density in the draining lymph nodes of restrained mice probably was responsible for the diminished IL-2 response as the absolute number of virus-specific T cells in the node was significantly different from that in the control (46).

Whereas physical restraint had a profound effect on virus-specific cytokine responses, the titers of antiinfluenza antibody 10 days postinfection were similar in restrained and control animals (143). However, when the kinetics and isotype switching were studied during influenza virus infection, it was determined that physical restraint altered the kinetics of the antibody response. Seroconversion in the immunoglobulin M (IgM) isotype was delayed by restraint, and isotype switching from IgM to IgG and from IgG to IgA was significantly delayed (Fig. 5). Ultimately, however, restraint did not alter the magnitude or class of the humoral response (47).

As mentioned previously, restraint stress reduced the level of mononuclear infiltration in the lungs and, in addition, the cell densities of the draining lymph nodes (superficial cervical and mediastinal lymph nodes) were markedly reduced (46, 76). Reduced inflammation in the lung was not due to an effect of restraint stress on virus replication in the lungs as the kinetics and titers of influenza virus in restrained and control mice were not significantly different (46).

Restraint and restraint plus infection markedly elevated plasma corticosterone levels (143). To determine the role of corticosterone in suppression of the lymphadenopathy response, mice were adrenalectomized 2 weeks prior to restraint and infection. Mice receiving sham surgeries served as a control. Adrenalectomy restored the cellularity of the mediastinal lymph node in restraint-stressed mice, thus suggesting that reduced cellularity in the node was adrenal-corticosterone dependent (46). To summarize our observations in the influenza virus model, it is clear that restraint stress altered the pathology observed in the lungs of infected animals and reduced the cellular immune response, as reflected in diminished IL-2 responses in stressed mice. Pharmacologic approaches are currently being employed to delineate the roles of neuroendocrine hormones and transmitters in restraint stress-induced modulation of viral pathogenesis and immunity to influenza virus.

We have also studied the effects of restraint stress on a mouse footpad infection model with HSV-1 strain Patton. Restraint reduced the cell yields from the draining lymph nodes (popliteal) as well as the virus-specific IL-2 T-cell

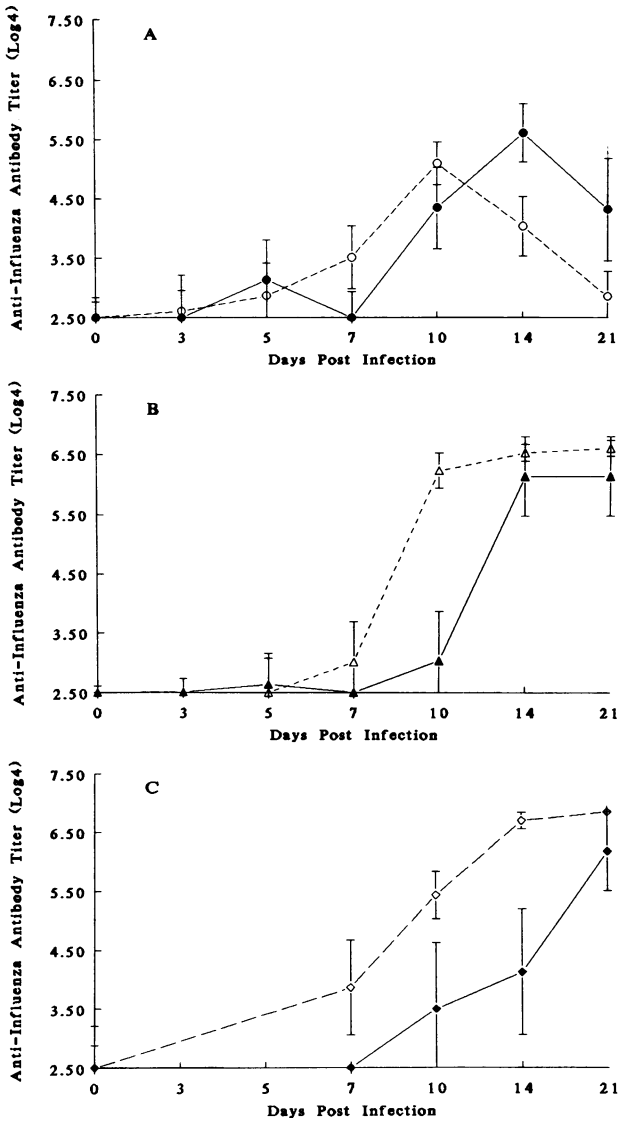

FIG. 5. Effects of restraint stress on antiinfluenza antibody titer. Mice were restrained 1 day prior to infection and then restrained 14 consecutive days postinfection (numbers of mice per time point were 10, 5, 5, 5, and 6 for days 0, 7, 10, 14, and 21 postinfection, respectively). Control mice were infected but not restrained (numbers of mice per time point were 9, 4, 5, 5, and 5 for days 0, 7, 10, 14, and 21 postinfection, respectively). Sera were collected and assayed for A/PR8-specific IgM (A [●, restraint; ○, no restraint]), IgG (B [▲, restraint; △, no restraint]) and IgA (C [◆, restraint; ◇, no restraint]) antibodies. Analysis of variance revealed significant day-treatment group interactions for all three antibody isotypes tested. Each datum point represents the mean antibody titer ± standard error of the mean. Reprinted from reference 47 with permission of the publisher.

responses. Cytotoxic responses of NK cells and $CD8^+$ T cells were also suppressed by restraint (12). This probably accounted for the higher titers of HSV-1 in the footpads of the restrained mice. Restraint had a differential effect on the T-cell subsets ($CD4^+$ and $CD8^+$ T cells). Restraint diminished the IL-2 response in the draining lymph node, but the frequencies of virus-specific IL-2-secreting T cells were similar in control and restrained groups, as observed in the influenza virus model. Restraint also diminished the cytolytic activity of class

I-restricted CTL recovered from the nodes; however, the frequency of CTL precursors in the node was reduced. The effects of restraint on the development of HSV-specific memory CTL (CTLm) responses was examined, as was the effect of stress on HSV-specific CTLm localization and proliferation in the popliteal lymph node following reexposure to HSV. Restraint stress did not inhibit the generation of CTLm; however, it did inhibit the ability to activate CTLm to the lytic phenotype. Furthermore, in mice primed to HSV prior to restraint, the application of the stressor prevented in vivo activation and/or migration of HSV-specific CTLm in the popliteal lymph nodes. These findings suggest that virus-specific immunological memory can be inhibited by physiological changes associated with experimental stressors. Further, it is possible that such immune inhibition may provide a mechanism that accounts for the development of recrudescent herpetic disease (13).

Adrenalectomy restored the generation of HSV-specific CTL in the lymph nodes of restrained mice. However, administration of exogenous corticosterone alone to adrenalectomized mice did not suppress CTL generation (14). An adrenal-independent mechanism induced by restraint synergized with corticosterone to suppress CTL development. This study suggests that both adrenal-dependent and -independent mechanisms contribute to stress-induced modulation of HSV immunity. Similar observations of depressed cell-mediated immune responses and increased pathogenicity were made in the murine HSV-1 model when mild electric shock was used as the stressor (104).

In recent studies designed to elucidate the mechanisms of stress-induced immunomodulation, treatment of restrained, HSV-infected animals with a GC receptor antagonist (RU486) restored the cellularity of the draining popliteal lymph nodes, but cytolytic T-cell activation in the lymph node remained depressed. On the other hand, treatment of these mice with nadolol (a beta-adrenergic receptor antagonist) partially restored cytolytic T-cell activity but failed to increase the cellularity of the popliteal node. However, treatment of restrained mice with a combination of the two drugs completely restored HSV-specific CTL activity to the popliteal lymph node (37).

CONCLUSIONS

Overall, the human and animal research reviewed in this article demonstrates the important health consequences of stress. These data provide evidence for an association between stress and the pathogenesis of infectious disease and suggest that the effects of stress on infectious disease are mediated through the neuroendocrine-immune interactions. Though there is abundant in vitro research demonstrating that products of the HPA axis and the SNS can modulate in vitro correlates of immune function, there is limited in vivo research exploring such modulation in the context of infectious disease. Further studies exploring the effects of neuroendocrine-immune interactions on microbial pathogenesis and immunity during an infectious disease are needed to dissect the mechanisms by which stress modulates these processes.

ACKNOWLEDGMENTS

This work was supported, in part, by grants from the National Institutes of Health to J.F.S. (HL38485 and MH46801) and to B.Z. (MH45679 and AA09321).

REFERENCES

1. **Abrass, C. K., S. W. O'Connor, P. J. Scarpace, and I. B. Abrass.** 1985. Characterization of the β-adrenergic receptor of the rat peritoneal macrophage. J. Immunol. **135**:1338–1341.
2. **Ader, R., D. L. Felten, and N. Cohen.** 1991. Preface, p. xxv–xxvii. *In* R. Ader, D. L. Felten, and N. Cohen (ed.), Psychoneuroimmunology, 2nd ed. Academic Press, Inc., San Diego, Calif.
3. **An, S. H., F. J. DePauli, P. Wright, and D. G. Ingram.** 1978. Characteristics of inapparent Aleutian disease virus infection in mink. Res. Vet. Sci. **24**:200–204.
4. **Ausiello, C. M., and L. G. Roda.** 1984. Leu-enkephalin binding to cultured human T-lymphocytes. Cell. Biol. Int. Rep. **8**:353–362.
5. **Axelrod, J., and T. D. Reisine.** 1984. Stress hormones: their interaction and regulation. Science **224**:452–459.
6. **Beard, C. W., and B. W. Mitchell.** 1987. Effects of environmental temperatures on the serologic responses of broiler chickens to inactivated and viable Newcastle disease vaccines. Avian Dis. **31**:321–326.
7. **Ben-Nathan, D., and G. Feuerstein.** 1990. The influence of cold or isolation stress on resistance of mice to West Nile virus encephalitis. Experientia **46**:285–290.
8. **Ben-Nathan, D., S. Lustig, and H. D. Danenberg.** 1991. Stress-induced neuroinvasiveness of a neurovirulent noninvasive Sindbis virus in cold or isolation subjected mice. Life Sci. **48**:1493–1500.
9. **Ben-Nathan, D., S. Lustig, and G. Feuerstein.** 1989. The influence of cold or isolation stress on neuroinvasiveness and virulence of an attenuated variant of West Nile virus. Arch. Virol. **109**:1–10.
10. **Beutler, B., N. Krochin, I. W. Milsark, C. Luedke, and A. Cerami.** 1986. Control of cachectin (tumor necrosis factor) synthesis: mechanisms of endotoxin resistance. Science **232**:977–980.
11. **Blackwell, G. J., and R. J. Flower.** 1983. Inhibition of phospholipase activity. Br. Med. Bull. **39**:260–264.
12. **Bonneau, R. H., J. F. Sheridan, N. Feng, and R. Glaser.** 1991. Stress-induced suppression of herpes simplex virus (HSV)-specific cytotoxic T lymphocyte and natural killer cell activity and enhancement of acute pathogenesis following local HSV infection. Brain Behav. Immun. **5**:170–192.
13. **Bonneau, R. H., J. F. Sheridan, N. Feng, and R. Glaser.** 1991. Stress-induced effects on cell-mediated innate and adaptive memory components of the murine response to herpes simplex virus infection. Brain Behav. Immun. **5**:274–295.
14. **Bonneau, R. H., J. F. Sheridan, N. Feng, and R. Glaser.** 1993. Stress-induced modulation of the primary cellular immune response to herpes simplex virus is mediated by both adrenal-dependent and adrenal-independent mechanisms. J. Neuroimmunol. **42**:167–176.
15. **Bost, K. L., E. M. Smith, L. B. Wear, and J. E. Blalock.** 1987. Presence of ACTH and its receptors on a B lymphocytic cell line: a possible autocrine function for a neuroendocrine hormone. J. Biol. Regul. Homeostat. Agents **1**:23–27.
16. **Broadbent, D. E., M. H. P. Broadbent, R. J. Phillpotts, and J. Wallace.** 1984. Some further studies on the prediction of experimental colds in volunteers by psychological factors. J. Psychosom. Res. **28**:511–523.
17. **Brooks, W. H., R. J. Cross, T. L. Roszman, and W. R. Markesbery.** 1982. Neuroimmunomodulation: neural anatomical basis for impairment and facilitation. Ann. Neurol. **12**:56–61.
18. **Brown, D. H., J. Sheridan, D. Pearl, and B. S. Zwilling.** 1993. Regulation of mycobacterial growth by the hypothalamus-pituitary-adrenal axis: differential responses of *Mycobacterium bovis* BCG-resistant and -susceptible mice. Infect. Immun. **61**:4793–4800.
19. **Brown, S. L., and D. E. Van Epps.** 1986. Opioid peptides modulate production of interferon γ by human mononuclear cells. Cell. Immunol. **103**:19–26.
20. **Carr, D. J., B. R. DeCosta, A. E. Jacobsen, K. C. Rice, and J. E. Blalock.** 1990. Corticotropin-releasing hormone augments natural killer cell activity through a naloxone-sensitive pathway. J. Neuroimmunol. **28**:53–61.
21. **Carr, D. J., and G. R. Klimpel.** 1986. Enhancement of the generation of cytotoxic T cells by endogenous opiates. J. Neuroimmunol. **12**:75–87.
22. **Chang, S.-S., and A. F. Rasmussen.** 1965. Stress-induced suppression of interferon production in virus-infected mice. Nature (London) **205**:623–624.

23. **Chester, A. C.** 1992. Psychological stress and the common cold. N. Engl. J. Med. **326**:644–645. (Letter; comment.)
24. **Chetverikova, L. K., B. A. Frolov, T. A. Kramskaya, and R. Y. A. Polyak.** 1987. Experimental influenza infection: influence of stress. Acta Virol. **31**:424–433.
25. **Chung, H., W. E. Samlowski, and R. A. Daynes.** 1986. Modification of the murine immune system by glucocorticoids: alterations of the tissue localization properties of circulating lymphocytes. Cell. Immunol. **101**:571–585.
26. **Clover, R. D., T. Abell, L. A. Becker, S. Crawford, and C. N. Ramsey.** 1989. Family functioning and stress as predictors of influenza B infection. J. Fam. Pract. **28**:535–539.
27. **Cohen, S., D. A. J. Tyrrell, and A. P. Smith.** 1991. Psychological stress and susceptibility to the common cold. N. Engl. J. Med. **325**:606–612.
28. **Coker, C. M.** 1956. Cellular factors in acquired immunity to *Trichinella spiralis* as indicated by cortisone treatment of mice. J. Infect. Dis. **98**:187–197.
29. **Coker, C. M.** 1956. Some effects of cortisone in mice with acquired immunity to *Trichinella spiralis*. J. Infect. Dis. **98**:39–44.
30. **Collins, F. M.** 1989. Mycobacterial disease: immunosuppression and acquired immunodeficiency syndrome. Clin. Microbiol. Rev. **2**:360–377.
31. **Corey, L., and P. G. Spear.** 1986. Infections with herpes simplex virus. N. Engl. J. Med. **314**:749–757.
32. **Crabtree, G. R., A. Munck, and K. A. Smith.** 1980. Glucocorticoids and lymphocytes. I. Increased glucocorticoid receptor levels in antigen stimulated lymphocytes. J. Immunol. **124**:2430–2435.
33. **Crowle, A. J., and N. Elkins.** 1990. Relative permissiveness of macrophages from black and white people for virulent tubercle bacilli. Infect. Immun. **58**:632–638.
34. **Dannenberg, A. M.** 1993. Immunopathogenesis of pulmonary tuberculosis. Hosp. Pract., January 15, p. 33–40.
35. **Denis, M., A. Forget, M. Pelletier, and E. Skamene.** 1988. Pleiotropic effects of the Bcg gene. I. Antigen presentation in genetically susceptible and resistant congenic mouse strains. J. Immunol. **140**:2395–2400.
36. **Denis, M., A. Forget, M. Pelletier, and E. Skamene.** 1988. Pleiotropic effects of the Bcg gene. III. Respiratory burst in Bcg congenic macrophages. Clin. Exp. Immunol. **73**:370–375.
37. **Dobbs, C. M., M. Vasquez, R. Glaser, and J. F. Sheridan.** 1993. Mechanisms of stress-induced modulation of viral pathogenesis and immunity. J. Neuroimmunol. **48**:151–160.
38. **Droz, B., and C. P. Leblond.** 1962. Migration of proteins along the axons of the sciatic nerve. Science **137**:1047–1048.
39. **Edwards, E. A., and L. M. Dean.** 1977. Effects of crowding of mice on humoral antibody formation and protection to lethal antigenic challenge. Psychosom. Med. **39**:19–24.
40. **Eguchi, K., A. Kawakami, M. Nakashima, H. Ida, S. Sakito, N. Matsuoka, K. Terada, M. Sakai, Y. Kawabe, T. Fukuda, T. Ishimaru, K. Kurouji, N. Fujita, T. Aoyagi, K. Maeda, and S. Nagataki.** 1992. Interferon-alpha and dexamethasone inhibit adhesion of T cells to endothelial cells and synovial cells. Clin. Exp. Immunol. **88**:448–454.
41. **Eipper, B. A., and R. E. Mains.** 1980. Structure and biosynthesis of proadrenocorticotropin/endorphin and related peptides. Endocrinol. Rev. **1**:1–27.
42. **Faith, R. E., H. J. Liang, A. J. Murgo, and N. P. Plotnikoff.** 1984. Neuroimmunomodulation with enkephalins: enhancement of human natural killer (NK) cell activity in vitro. Clin. Immunol. Immunopathol. **31**:412–418.
43. **Fauci, A. S.** 1975. Mechanisms of corticosteroid action on lymphocyte subpopulations. I. Redistribution of circulating T and B lymphocytes to the bone marrow. Immunology **28**:669–680.
44. **Felten, S. Y., and D. L. Felten.** 1991. Innervation of lymphoid tissue, p. 27–69. *In* R. Ader, D. L. Felten, and N. Cohen (ed.), Psychoneuroimmunology, 2nd ed. Academic Press, Inc., San Diego, Calif.
45. **Felten, S. Y., and J. A. Olschowka.** 1987. Noradrenergic sympathetic innervation of the spleen. II. Tyrosine hydroxylase (TH)-positive nerve terminals from synaptic-like contacts on lymphocytes in the splenic white pulp. J. Neurosci. Res. **18**:37–48.
46. **Feng, N.** 1992. Restraint stress-induced alteration of the pathogenesis and immune response to influenza virus infection in mice. Ph.D. dissertation. Ohio State University, Columbus.
47. **Feng, N., R. Pagniano, C. A. Tovar, R. H. Bonneau, and J. F. Sheridan.** 1991. The effect of restraint stress on the kinetics, magnitude, and isotype of the humoral immune response to influenza virus infection. Brain Behav. Immun. **4**:370–382.
48. **Filion, L. G., P. J. Willson, H. Bielefeldt-Ohmann, L. A. Babiuk, and R. G. Thomson.** 1984. The possible role of stress in the induction of pneumonic pasteurellosis. Can. J. Comp. Med. **48**:268–274.
49. **Forget, A., E. Skamene, P. Gros, A. C. Miailke, and R. Turcotte.** 1981. Differences in response among inbred mouse strains to infection with small doses of *Mycobacterium bovis*. Infect. Immun. **32**:42–47.
50. **Friedman, S. B., R. Ader, and L. J. Grota.** 1973. Protective effect of noxious stimulation in mice infected with rodent malaria. Psychosom. Med. **35**:535–537.
51. **Friedman, S. B., L. A. Glasgow, and R. Ader.** 1970. Differential susceptibility to a viral agent in mice housed alone or in groups. Psychosom. Med. **32**:285–299.
52. **Frohman, E. M., B. Vayuvegula, S. Gupta, and S. van den Noort.** 1988. Norepinephrine inhibits gamma-interferon-induced major histocompatibility class II (Ia) antigen expression on cultured astrocytes via beta-2-adrenergic signal transduction mechanisms. Proc. Natl. Acad. Sci. USA **85**:1292–1296.
53. **Fuchs, B. A., J. W. Albright, and J. F. Albright.** 1988. β-Adrenergic receptors on murine lymphocytes: density varies with cell maturity and lymphocyte subtype and is decreased after antigen administration. Cell. Immunol. **114**:231–245.
54. **Gaitman, B. G., J. L. Chason, and A. M. Lerner.** 1970. Augmentation of the virulence of murine coxsackievirus B-3 myocardiopathy by exercise. J. Exp. Med. **131**:1121–1136.
55. **Galant, S. P., L. Durisetti, S. Underwood, and P. A. Insel.** 1978. β-Adrenergic receptors on polymorphonuclear leukocytes: adrenergic therapy decreases receptor number. N. Engl. J. Med. **299**:933–936.
56. **Gilman, S. C., J. M. Schwartz, R. J. Milner, F. E. Bloom, and J. D. Feldman.** 1982. β-Endorphin enhances lymphocyte proliferative responses. Proc. Natl. Acad. Sci. USA **79**:4226–4230.
57. **Gilmore, W., and L. P. Weiner.** 1988. β-Endorphin enhances interleukin-2 (IL-2) production in murine lymphocytes. J. Neuroimmunol. **18**:125–138.
58. **Gilmore, W., and L. P. Weiner.** 1989. The opioid specificity of beta-endorphin enhancement of murine lymphocyte proliferation. Immunopharmacology **17**:19–30.
59. **Glaser, R., and T. E. Gotleib-Stematsky.** 1982. Human herpesvirus infections: clinical aspects. Marcel Decker, New York.
60. **Glaser, R., J. K. Kielcolt-Glaser, R. H. Bonneau, W. Malarkey, S. Kennedy, and J. Hughes.** 1992. Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. Psychosom. Med. **54**:22–29.
61. **Glaser, R., J. K. Kielcolt-Glaser, C. E. Speicher, and J. E. Holliday.** 1985. Stress, loneliness, and changes in herpesvirus latency. J. Behav. Med. **8**:249–260.
62. **Goldmeier, D., and A. Johnson.** 1982. Does psychiatric illness affect the recurrence rate of genital herpes? Br. J. Vener. Dis. **58**:40–43.
63. **Goodkin, K., I. Fuchs, D. Feaster, J. Leeka, and D. D. Rishel.** 1992. Life stressors and coping style are associated with immune measures in HIV-1 infection—a preliminary report. Int. J. Psychiatry Med. **22**:155–172.
64. **Grabstein, K., S. Dower, S. Gillis, D. Urdal, and A. Larsen.** 1986. Expression of interleukin 2, interferon-γ, and the IL-2 receptor by human peripheral blood lymphocytes. J. Immunol. **136**:4503–4508.
65. **Graham, N. M. H., R. M. Douglas, and P. Ryan.** 1986. Stress and acute respiratory infection. Am. J. Epidemiol. **124**:389–401.
66. **Green, G. M., and E. H. Kass.** 1965. The influence of bacterial species on pulmonary resistance to infection in mice subjected to hypoxia, cold stress and ethanol intoxication. Br. J. Exp. Pathol. **46**:360–366.
67. **Gros, P., E. Skamene, and A. Forget.** 1981. Genetic control of natural resistance to *Mycobacterium bovis* (BCG) in mice. J.

Immunol. **127:**2417–2421.
68. **Gross, W. B.** 1984. Effect of a range of social stress severity on *Escherichia coli* challenge infection. Am. J. Vet. Res. **45:**2074–2076.
69. **Gross, W. B.** 1988. Effect of environmental stress on the response of ascorbic-acid treated chickens to *Escherichia coli* challenge infections. Avian Dis. **32:**432–436.
70. **Gross, W. B.** 1989. Effect of adrenal blocking chemicals on viral and respiratory infections of chickens. Can. J. Vet. Res. **53:**48–51.
71. **Gross, W. B., and C. H. Domermuth.** 1988. Factors influencing the severity of *Escherichia coli* and avian adenovirus group II infections in chickens. Avian Dis. **32:**793–797.
72. **Gross, W. B., J. D. Falkinham III, and J. B. Payeur.** 1989. Effect of environmental-genetic interactions on *Mycobacterium avium* challenge infection. Avian Dis. **33:**411–415.
73. **Hall, N. R., J. E. McClure, S. K. Hu, N. S. Tare, C. M. Selas, and A. L. Goldstein.** 1982. Effects of 6-hydroxydopamine upon primary and secondary thymus dependent immune responses. Immunopharmacology **5:**39–48.
74. **Hamilton, D. R.** 1974. Immunosuppressive effects of predator induced stress in mice with acquired immunity to *Hymenolepis nana*. J. Psychosom. Res. **18:**143–153.
75. **Hassan, N. F., and S. D. Douglas.** 1990. Stress-related neuroimmunomodulation of monocyte-macrophage functions in HIV-1 infection. Clin. Immunol. Immunopathol. **54:**220–227.
76. **Hermann, G., C. A. Tovar, F. M. Beck, C. Allen, and J. F. Sheridan.** 1993. Restraint stress differentially affects the pathogenesis of an experimental influenza viral infection in three inbred strains of mice. J. Neuroimmunol. **47:**83–94.
77. **Holt, P. S.** 1993. Effect of induced molting on the susceptibility of white leghorn hens to a *Salmonella enteritidis* infection. Avian Dis. **37(2):**412–417.
78. **Holt, P. S., and R. E. Porter.** 1992. Microbiological and histopathological effects of an induced-molt fasting procedure on a *Salmonella enteritidis* infection in chickens. Avian Dis. **36:**610–618.
79. **Ilback, N.-G., J. Fohlman, and G. Friman.** 1989. Exercise in coxsackie B3 myocarditis: effects on heart lymphocyte subpopulations and the inflammatory reaction. Am. Heart J. **117:**1298–1302.
80. **Ilback, N.-G., G. Friman, W. Beisel, A. J. Johnson, and R. F. Berendt.** 1984. Modifying effects of exercise on clinical course and biochemical response of the myocardium in influenza and tularemia in mice. Infect. Immun. **45:**498–504.
81. **Ironson, G., A. LaPerriere, M. Antoni, P. O'Hearn, N. Schneiderman, N. Klimas, and M. A. Fletcher.** 1990. Changes in immune and psychological measures as a function of anticipation and reaction to news of HIV-1 antibody status. Psychosom. Med. **52:**247–270.
82. **Irwin, M. R., and R. L. Hauger.** 1988. Adaptation to chronic stress: temporal pattern of immune and neuroendocrine correlates. Neuropsychopharmacology **1:**239–243.
83. **Irwin, M. R., R. L. Hauger, M. Brown, and K. T. Britton.** 1988. CRF activates the autonomic nervous system and reduces natural killer cytotoxicity. Am. J. Physiol. **255:**R744–747.
84. **Irwin, M. R., W. Vale, and K. T. Britton.** 1987. Central corticotropin-releasing factor suppresses natural killer cytotoxicity. Brain Behav. Immun. **1:**81–87.
85. **Ishigami, T.** 1919. The influence of psychic acts on the progress of pulmonary tuberculosis. Am. Rev. Tuberculosis **2:**470–484.
86. **Jackson, G. J.** 1955. The effect of cortisone on *Plasmodium berghi* infections in the white rat. J. Infect. Dis. **97:**152–159.
87. **Jensen, M. M., and A. F. Rasmussen.** 1963. Stress and susceptibility to viral infections. II. Sound stress and susceptibility to vesicular stomatitis virus. J. Immunol. **90:**21–23.
88. **Johnson, E. W., J. E. Blalock, and E. M. Smith.** 1988. ACTH receptor-mediated induction of leukocyte cyclic AMP. Biochem. Biophys. Res. Commun. **157:**1205–1211.
89. **Johnson, H. M., E. M. Smith, B. A. Torres, and J. E. Blalock.** 1982. Regulation of the *in vitro* antibody response by neuroendocrine hormones. Proc. Natl. Acad. Sci. USA **79:**4171–4174.
90. **Johnson, H. M., B. A. Torres, E. M. Smith, L. D. Dion, and J. E. Blalock.** 1984. Regulation of lymphokine (interferon-γ) production by corticotropin. J. Immunol. **132:**246–250.
91. **Johnson, S. C., and B. S. Zwilling.** 1985. Continuous expression of I-A antigen by peritoneal macrophages from mice resistant to *Mycobacterium bovis* (BCG). J. Leukocyte Biol. **38:**635–645.
92. **Johnsson, T., J. F. Lavender, E. Hultin, and A. F. Rasmussen.** 1963. The influence of avoidance-learning stress on resistance of mice to coxsackie B virus in mice. J. Immunol. **91:**569–575.
93. **Kemeny, M. E., F. Cohen, L. S. Zegans, and M. A. Conant.** 1989. Psychological and immunological predictors of genital herpes recurrence. Psychosom. Med. **58:**195–208.
94. **Kern, J. A., R. J. Lamb, J. C. Reed, R. P. Daniele, and P. C. Nowell.** 1988. Dexamethasone inhibition of interleukin 1 beta production by human monocytes. J. Clin. Invest. **81:**237–244.
95. **Kessler, R. C., C. Foster, J. Joseph, D. Ostrow, C. Wortman, J. Phair, and J. Chmiel.** 1991. Stressful life events and symptom onset in HIV infection. Am. J. Psychiatry **148:**733–738.
96. **Kiecolt-Glaser, J. K., J. R. Dura, C. E. Speicher, O. J. Trask, and R. Glaser.** 1991. Spousal caregivers of dementia victims: longitudinal changes in immunity and health. Psychosom. Med. **53:**345–362.
97. **Kiecolt-Glaser, J. K., L. D. Fisher, P. Ogrocki, J. C. Stout, C. E. Speicher, and R. Glaser.** 1987. Marital quality, marital disruption, and immune function. Psychosom. Med. **49:**13–34.
98. **Kielcolt-Glaser, J. K., and R. Glaser.** 1988. Psychological influences on immunity: implications for AIDS. Am. Psychologist **43:**892–898.
99. **Kiecolt-Glaser, J. K., R. Glaser, E. C. Shuttleworth, C. S. Dyer, P. Ogrocki, and C. E. Speicher.** 1987. Chronic stress and immunity in family caregivers of Alzheimer's disease victims. Psychosom. Med. **49:**523–535.
100. **Kiecolt-Glaser, J. K., S. Kennedy, S. Malkoff, L. Fisher, C. E. Speicher, and R. Glaser.** 1988. Marital discord and immunity in males. Psychosom. Med. **50:**213–229.
101. **Kochi, A.** 1991. The global tuberculosis situation and the new control strategy of the World Health Organization. Tubercule **72:**1–6.
102. **Koff, W. C., and M. A. Dunegan.** 1985. Modulation of macrophage-mediated tumoricidal activity by neuropeptides and neurohormones. J. Immunol. **135:**350–354.
103. **Krieger, D. T.** 1983. Brain peptides: what, where, and why? Science **222:**975–985.
104. **Kusnecov, A. V., L. J. Grota, S. G. Schmidt, R. H. Bonneau, J. F. Sheridan, R. Glaser, and J. A. Moynihan.** 1992. Decreased herpes simplex viral immunity and enhanced pathogenesis following stressor administration in mice. J. Neuroimmunol. **38:**129–138.
105. **Landmann, R., E. Burgisser, M. West, and F. R. Buhler.** 1985. β-Adrenergic receptors are different in subpopulations of human circulating lymphocytes. J. Receptor Res. **4:**37–50.
106. **Lee, S. W., A.-P. Tso, H. Chan, J. Thomas, K. Petrie, E. M. Eugui, and A. C. Allison.** 1988. Glucocorticoids selectively inhibit the transcription of the interleukin 1 β gene and decrease the stability of interleukin 1 β mRNA. Proc. Natl. Acad. Sci. USA **85:**1204–1208.
107. **Lew, W., J. J. Oppenheim, and K. Matsushima.** 1988. Analysis of the suppression of Il-1α and Il-1β production in human peripheral blood mononuclear adherent cells by a glucocorticoid hormone. J. Immunol. **140:**1895–1902.
108. **Livnat, S., S. Y. Felten, S. L. Carlson, D. L. Bellinger, and D. L. Felten.** 1985. Involvement of peripheral and central catecholamine systems in neural-immune interactions. J. Neuroimmunol. **10:**5–30.
109. **Livnat, S., K. S. Madden, D. L. Felten, and S. Y. Felten.** 1987. Regulation of the immune system by sympathetic neural mechanisms. Prog. Neuro-Psychopharmacol. Biol. Psychiatry **11:**145–152.
110. **Loveland, B. E., B. Jarrot, and I. F. C. McKenzie.** 1981. Beta-adrenergic receptors on murine lymphocytes. Int. J. Immunopharmacol. **3:**45–55.
111. **Madden, K. S., and S. Livnat.** 1991. Catecholamine action and immunologic reactivity, p. 283–310. *In* R. Ader, D. L. Felten, and N. Cohen (ed.), Psychoneuroimmunology, 2nd ed. Academic Press, Inc., San Diego, Calif.
112. **Mains, R. E., and B. A. Eipper.** 1981. Synthesis and secretion of

ACTH, β-endorphin and related peptides. Adv. Biochem. Psychopharmacol. **28:**35–47.
113. **Mandler, R. N., W. E. Biddison, R. Mandler, and S. A. Serrate.** 1986. β-Endorphin augments the cytolytic activity and interferon production of natural killer cells. J. Immunol. **136:**934–939.
114. **Matthews, P. M., C. J. Froelich, W. L. Sibbitt, and A. D. Bankhurst.** 1983. Enhancement of natural cytotoxicity by β-endorphin. J. Immunol. **130:**1658–1662.
115. **McCain, H. W., I. B. Lamster, and J. Bilotta.** 1986. Modulation of human T-cell suppressor activity by beta endorphin and glycyl-L-glutamine. Int. J. Immunopharmacol. **8:**443–446.
116. **McCain, H. W., I. B. Lamster, J. M. Bozzone, and J. T. Grbic.** 1982. β-Endorphin modulates human immune activity via non-opiate receptor mechanisms. Life Sci. **31:**1619–1624.
117. **McKinnon, W., C. Weisse, C. P. Reynolds, C. A. Bowles, and A. Baum.** 1989. Chronic stress, leukocyte subpopulations, and humoral response to latent viruses. Health Psychol. **8:**389–402.
118. **McLean, R. G.** 1982. Potentiation of Keystone virus infection in cotton rats by glucocorticoid-induced stress. J. Wildl. Dis. **18:** 141–148.
119. **Mehrishi, J. N., and I. H. Mills.** 1983. Opiate receptors on lymphocytes and platelets in man. Clin. Immunol. Immunopathol. **27:**240–249.
120. **Melmon, K. L., H. R. Bourne, Y. Weinstein, G. M. Shearer, J. Kram, and S. Bauminger.** 1974. Hemolytic plaque formation by leukocytes in vitro—control by vasoactive hormones. J. Clin. Invest. **53:**13–21.
121. **Mohamed, M. A., and R. P. Hansen.** 1980. Effects of social stress on Newcastle disease virus (LaSota) infection. Avian Dis. **24:**908–915.
122. **Motulsky, H. J., and P. A. Insel.** 1982. Adrenergic receptors in man. N. Engl. J. Med. **307:**18–29.
123. **Munck, A., and P. M. Guyre.** 1991. Glucocorticoids and immune function, p. 447–474. *In* R. Ader, D. L. Felten, and N. Cohen (ed.), Psychoneuroimmunolgy, 2nd ed. Academic Press, Inc., San Diego, Calif.
124. **Northrop, J. P., G. R. Crabtree, and P. S. Mattila.** 1992. Negative regulation of interleukin 2 transcription by the glucocorticoid receptor. J. Exp. Med. **175:**1235–1245.
125. **Ozherelkov, S. V., V. V. Khozinsky, and B. F. Semenov.** 1990. Replication of Langat virus in immunocompetent cells of mice subjected to immobilization stress. Acta Virol. **34:**291–294.
126. **Payne, F. E., A. Larson, D. L. Walker, L. Foster, and K. F. Meyer.** 1955. Studies on immunization against plague. IX. The effects of cortisone on mouse resistance to attenuated strains of *Pasteurella pestis*. J. Infect. Dis. **96:**168–173.
127. **Perry, S., B. Fishman, L. Jacobsberg, and A. Frances.** 1992. Relationships over one year between lymphocyte subsets and psychosocial variables among adults with infection by human immunodeficiency virus. Arch. Gen. Psychiatry **49:**396–401.
128. **Petry, L. J., L. B. Weems III, and J. N. Livingstone.** 1993. Relationship of stress, distress, and the immunologic response to a recombinant hepatitis B vaccine. J. Fam. Pract. **32:**481–486.
129. **Pitchenik, A. E., and D. Fertel.** 1992. Tuberculosis and nontuberculosis mycobacterial disease. Med. Clin. N. Am. **76:**121–171.
130. **Potter, M., A. D. O'Brian, E. Skamene, P. Gros, A. Forget, P. A. L. Kongshavn, and J. S. Wax.** 1983. A BALB/c congenic strain of mice that carries a genetic locus (Ity^r) controlling resistance to intracellular parasites. Infect. Immun. **40:**1234–1235.
131. **Ramsey, J. M.** 1982. Basic pathophysiology: modern stress and the disease process, p. 30–73. Addison-Wesley Publishing Co., Menlo Park, Calif.
132. **Rand, K. H., E. F. Hoon, J. K. Massey, and J. H. Johnson.** 1990. Daily stress and recurrence of genital herpes simplex. Arch. Intern. Med. **150:**1889–1893.
133. **Rasmussen, A. F., J. T. Marsh, and N. Q. Brill.** 1957. Increased susceptibility to herpes simplex in mice subjected to avoidance-learning stress or restraint. Proc. Soc. Exp. Biol. Med. **96:**183–189.
134. **Reyes, M. P., and A. M. Lerner.** 1976. Interferon and neutralizing antibody in sera of exercised mice with coxsackievirus B-3 myocarditis (39204). Proc. Soc. Exp. Biol. Med. **151:**333–338.
135. **Rivier, C., M. Brownstein, J. Speiss, J. Rivier, and W. Vale.** 1982. In vivo corticotropin-releasing factor-induced secretion of adrenocorticotropin, beta-endorphin, and corticosterone. Endocrinology **110:**272–278.
136. **Robson, J. M., and K. A. Didcock.** 1956. The action of cortisone on corneal tuberculosis studied with the phase contrast microscope. Am. Rev. Tuberc. Pulm. Dis. **74:**1–6.
137. **Roizman, B.** 1990. Herpesviridae: a brief introduction, p. 1787–1793. *In* B. N. Fields and D. M. Knipe (ed.), Virology, 2nd ed. Raven Press, New York.
138. **Rosenbaum, H. E., and C. G. Harford.** 1953. Effects of fatigue on the susceptibility of mice to poliomyelitis. Proc. Soc. Exp. Biol. Med. **83:**678–681.
139. **Sadeghi, R., M. Feldman, and C. Hawrylowicz.** 1992. Upregulation of HLA class II, but not intercellular adhesion molecule I (ICAM-1) by granulocyte-macrophage colony stimulating factor (GM-CSF) or interleukin-3 (IL-3) in synergy with dexamethasone. Eur. Cytokine Netw. **3:**373–380.
140. **Schmidt, D. D., S. Zyzanski, J. Ellner, M. L. Kumar, and J. Arno.** 1985. Stress as a precipitating factor in subjects with recurrent herpes labialis. J. Fam. Pract. **4:**359–366.
141. **Schurr, E., E. Skamene, M. Nesbett, R. Hynes, and P. Gros.** 1988. Identification of a linkage group including the Bcg gene by restriction length polymorphism analysis. Curr. Top. Microbiol. Immunol. **137:**310–315.
142. **Shavit, Y., J. W. Lewis, G. W. Terman, R. P. Gale, and J. C. Liebeskind.** 1984. Opioid peptides mediate the suppressive effect of stress on natural killer cell cytotoxicity. Science **223:**188–190.
143. **Sheridan, J. F., N. Feng, R. H. Bonneau, C. M. Allen, B. S. Huneycutt, and R. Glaser.** 1991. Restraint differentially affects anti-viral cellular and humoral immune responses in mice. J. Neuroimmunol. **31:**245–255.
144. **Shimizu, M., Y. Shimizu, and Y. Kodama.** 1978. Effects of ambient temperature on induction of transmissable gastroenteritis in feeder pigs. Infect. Immun. **21:**747–752.
145. **Silver, P. S., S. M. Auerbach, N. Vishniavsky, and L. G. Kaplowitz.** 1986. Psychological factors in recurrent genital herpes infection: stress, coping style, social support, emotional dysfunction, and symptom recurrence. J. Psychosom. Res. **30:**163–171.
146. **Singer, I.** 1954. The effect of cortisone on infections with *Plasmodium berghi* in the white mouse. J. Infect. Dis. **94:**164–172.
147. **Smith, E. M., P. Bronsan, W. J. Meyer, and J. E. Blalock.** 1987. An ACTH receptor on human mononuclear leukocytes. N. Engl. J. Med. **317:**1266–1269.
148. **Snyder, D. S., and E. R. Unanue.** 1982. Corticosteroids inhibit murine macrophage Ia expression and interleukin 1 production. J. Immunol. **129:**1803–1805.
149. **Solano, L., M. Costa, S. Salvati, R. Coda, F. Aiuti, I. Mezzaroma, and M. Bertini.** 1993. Psychosocial factors and clinical evolution in HIV-1 infection: a longitudinal study. J. Psychosom. Res. **37:**39–51.
150. **Stead, W. W., J. W. Senner, W. T. Reddick, and J. P. Lofgren.** 1990. Racial differences in susceptibility to infection by *Mycobacterium tuberculosis*. N. Engl. J. Med. **322:**422–427.
151. **Strom, T. B., C. B. Carpenter, M. R. Garovoy, K. F. Austen, J. P. Merrill, and M. Kaliner.** 1973. The modulating activity of cyclic nucleotides upon lymphocyte-mediated cytotoxicity. J. Exp. Med. **138:**381–393.
152. **Swartz, M. N.** 1991. Stress and the common cold. N. Engl. J. Med. **325:**654–655. (Editorial; comment.)
153. **Thiry, E., J. Saliki, M. Bublot, and P.-P. Pastoret.** 1987. Reactivation of infectious bovine rhinotracheitis virus by transport. Comp. Immunol. Microbiol. Infect. Dis. **10:**59–63.
154. **Vacca, A., S. Martinotti, I. Screpanti, M. Maroder, M. P. Fellis, A. R. Farina, A. Gismondi, A. Santoni, L. Frati, and A. Gulino.** 1990. Transcriptional regulation of the interleukin 2 gene by glucocorticoid hormones. J. Biol. Chem. **265:**8075–8080.
155. **Vale, W., J. Speiss, C. Rivier, and J. Rivier.** 1981. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and β-endorphin. Science **213:**1394–1397.
156. **VanderPlate, C., S. O. Aral, and L. Magder.** 1988. The relation-

ship among genital herpes virus, stress, and social support. Health Psychol. **7:**159–168.
157. **Vollmer, E. P.** 1951. The course of pneumoccal infection in mice during treatment with antibacterial substances and adrenocortical extract. J. Infect. Dis. **88:**27–31.
158. **Webster, E. L., G. Battaglia, and E. B. De Souza.** 1989. Functional corticotropin-releasing factor (CRF) receptors in mouse spleen: evidence from adenylate cyclase studies. Peptides **10:**395–401.
159. **Webster, E. L., D. E. Tracey, M. A. Jutila, S. A. Wolfe, Jr., and E. B. De Souza.** 1990. Corticotropin-releasing factor receptors in mouse spleen: identification of receptor-bearing cells as resident macrophages. Endocrinology **127:**440–452.
160. **Werb, Z., R. Foley, and A. Munck.** 1978. Interaction of glucocorticoids with macrophages—identification of glucocorticoid receptors in monocytes and macrophages. J. Exp. Med. **147:**1684–1694.
161. **Wiegeshaus, E., V. Balasubramanian, and D. W. Smith.** 1989. Immunity to tuberculosis from the perspective of pathogenesis. Infect. Immun. **57:**3671–3676.
162. **Yamada, A., M. M. Jensen, and A. F. Rasmussen.** 1964. Stress and susceptibility to viral infections. III. Antibody response and viral retention during avoidance learning stress. Proc. Soc. Exp. Biol. Med. **116:**677–680.
163. **Zamri-Saad, M., S. Jasni, A. B. Naridi, and A. R. Sheikh-Omar.** 1991. Experimental infection of dexamethasone-treated goats with *Pasteurella haemolytica* A2. Br. Vet. J. **147:**565–568.
164. **Zwilling, B. S., D. Brown, and D. Pearl.** 1992. Induction of major histocompatibility complex class II glycoproteins by interferon-γ: attenuation of the effects of restraint stress. J. Neuroimmunol. **37:**115–122.
165. **Zwilling, B. S., M. Dinkins, R. Christner, M. Faris, A. Griffin, M. Hilburger, M. McPeek, and D. Pearl.** 1990. Restraint stress induced suppression of major histocompatibility complex class II expression by murine peritoneal macrophages. J. Neuroimmunol. **29:**125–130.