Stress and Pathogenesis of Infectious Disease

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Despite inherent difficulties in defining and measuring stress, a scientific framework has been provided in recent years for understanding how disruptive life experiences might be translated into altered susceptibility to infectious diseases. Studies of the effects of stress on pathogenesis of infectious disease are highly relevant to assessment of the biological importance of the immune impairments that have been associated with stress. With a few notable exceptions, investigations of viral infections in humans and in animal models support the hypothesis that stress promotes the pathogenesis of such infections. Similar conclusions can be drawn from studies of bacterial infections in humans and animals and from a small number of studies of parasitic infections in rodent models. While many of these studies have substantial limitations, the data nonetheless suggest that stress is a potential cofactor in the pathogenesis of infectious disease. Given recent unprecedented advances in the neurosciences, in immunology, and in the field of microbial pathogenesis, the relationship between stress and infection should be a fruitful topic for interdisciplinary research.

"The toxin of fatigue has been demonstrated; but the poisons generated by evil temper and emotional excess over non-essentials have not yet been determined, although without a doubt they exist."
Elie Metchnikoff (1845–1916)

The origin of the concept of stress can be traced to Empedocles in the fifth century B.C.; however, Hans Selye, in the late 1930s, was the first person to use the term *stress* more or less as it is used today [1, 2]. While it is inherently difficult to define the term *stress*—in fact, many experts refuse to do so—the definition provided in *Webster's Medical Dictionary* ("a state of bodily or mental tension resulting from factors that tend to alter an existent equilibrium" [3]) is compatible with current usage by researchers in this field [2]. The factors that alter equilibrium, or the normal regulatory rhythms (homeostasis), are termed stressors and include a variety of psychological, environmental, and physiologic stimuli. The outcome of stress, i.e., regained homeostasis or distress (disease), is influenced by multiple variables, as depicted in figure 1.

The purpose of this review is to examine the evidence bearing on the question, Can stress operate as a cofactor in the pathogenesis of infectious diseases? Given the above definitions, infectious disease agents themselves represent common environmental stressors, and the host response that they provoke can be regarded as stress. Thus the issue to be addressed in this review will be whether additional stressors can influence the outcome of infectious disease.

The topic of this review is timely since in the past decade major advances have been made in characterizing the bidirectional interaction between the brain and the immune system. During this period no fewer than eight books [4–11] and two new journals [12, 13] that are devoted to various aspects of the "brain-immune axis" have appeared. From this body of work, it has been firmly established that the CNS and the immune system are connected. A large number of studies have demonstrated that a variety of psychological stressors, e.g., bereavement, academic pressure, and loss of self-esteem, can result in laboratory evidence of immunologic impairment; the anatomic structures within the nervous system and the neuroendocrine pathways involved in the mediation of these effects have been elucidated (reviewed in [14–19]). A number of stress-responsive neuropeptides and neurotransmitters have been shown to interact with immune cells in vitro, and these molecules have been proposed as mediators of stress-induced immunosuppression (table 1). Some of these peptides as well as other neurohormones such as melatonin [46], also have been shown to have immunoaugmenting or antistress effects. Communication of the immune system with the brain, on the other hand, has been shown to be mediated via a growing list of "immunotransmitters" (e.g., interleukin-1, interleukin-6, tumor necrosis factor-α, and interferons [14]) and may also involve several neuroendocrine hormones produced by the immune cells themselves [17].

Received 18 May 1990; revised 10 September 1990.
Grant support: U.S. Public Health Service grants DA-04196, DA-04381, and 271-89-8155.
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Reviews of Infectious Diseases 1991;13:710–20

0162-0886/91/1304-0048$02.00

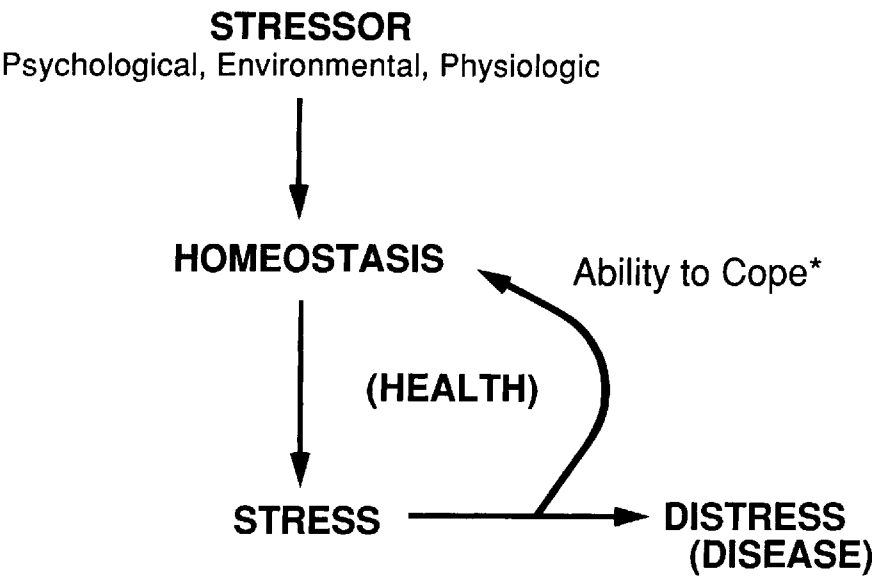

Figure 1. Stress is a state of altered homeostasis provoked by a psychological, environmental, or physiologic stressor.

The biologic significance of the findings in this area of research (psychoneuroimmunology) is less clear, however. The clinical importance of stress-related immunologic disturbance has been investigated in the fields of oncology, rheumatology, and allergy; however, investigations in the field of infectious diseases should yield especially relevant data given its large fund of knowledge regarding the impact of altered immune defenses on microbial pathogenesis. It is disappointing that there is a relative paucity of such data; in fact, most studies of stress and its pertinence to infectious diseases were performed before 1980. The scope of this review will be limited to the studies that have been carried out in mammals. While the use of animal models is distinctly advantageous in that it allows control of a number of important variables, as will be pointed out in this review, natural infections and naturally occurring stressors rarely have been selected for study in animals. In addition, the assessment of stress in animal models has been limited and in most cases has been largely inferential. Although natural infections and naturally occurring stressors have been examined in humans, there has been a lack of uniformity in the instruments used to measure stress, and often infection has not been microbiologically verified.

Table 1. Proposed mediators of stress-induced immunomodulation.

Mediator	[References]
Corticotropin-releasing factor, adrenocorticotropin, glucocorticoids	[20–23]
β-endorphin	[24–27]
Prolactin	[28–29]
Somatotropin	[30, 31]
Arginine vasopressin	[31, 32]
Norepinephrine, epinephrine	[33–37]
Enkephalin	[38, 39]
Substance P	[40–42]
Vasoactive intestinal peptide	[43–45]

Viral Infections

Animal Studies

The results of studies of the effect of stress on the pathogenesis of viral infection in animals are summarized in table 2. As shown, although a variety of viral pathogens have been studied, research in this area has been restricted primarily to rodent models. A number of stressors have been used: forced exercise (swimming or running in a motorized drum), avoidance learning (usually electric shock preceded by a warning stimulus), high-intensity sound, restraint, transportation, differential housing (isolation or crowding), and exposure to cold temperatures. Both the timing and the duration of exposure to the stressor relative to the initiation of infection have varied widely. The most commonly measured pathogenic effect has been altered survival of virus-infected animals.

As shown in table 2, mortality due to viral infection was found to be increased with almost all stressors studied. In a few instances, increased viral replication was noted, and in the cases of neurotropic and cardiotropic viruses, increased evidence of disease involving these organ systems was found. In only one study, of poliomyelitis virus in monkeys that were subjected to avoidance learning, did stress reduce mortality [49]. The fact that the same stressor increased the mortality

Table 2. Animal models of stress and viral infection.

Virus	Animal	Stressor	Finding	[Reference]
Poliomyelitis	Mouse	Forced exercise	↑ Mortality, paralysis	[47]
	Monkey	Forced exercise	↑ Paralysis	[48]
	Monkey	Avoidance learning	↓ Mortality	[49]
	Mouse	Avoidance learning	↑ Mortality, paralysis	[50]
Coxsackievirus B	Mouse	Avoidance learning	↑ Weight loss, viral dissemination	[51]
	Mouse	Avoidance learning	↑ Mortality, weight loss	[52]
	Mouse	Forced exercise	↑ Mortality, carditis	[53–55]
Vesicular stomatitis	Mouse	Sound	↑ Mortality	[56]
	Mouse	Avoidance learning	↑ Virus in muscle	[57]
	Mouse	Sound	↑ Mortality, encephalitis	[58]
Herpes simplex	Mouse	Avoidance learning	↑ Mortality	[59]
	Mouse	Restraint	↑ Mortality	[59]
Bovine herpesvirus 1	Calves	Transportation	↑ Mortality, pneumonia	[60]
Influenza A	Mouse	Forced exercise	↑ Mortality	[61]
Encephalomyocarditis	Mouse	Isolation	↑ Mortality	[62]
Rabies	Guinea pig	Crowding	Viral reactivation	[63]
Coronavirus	Swine	Cold	↑ Gastroenteritis	[64]

NOTE. ↑ = increased; ↓ = decreased.

of mice infected with poliomyelitis virus [50] suggests that the effect of stress may be animal species-dependent. Friedman et al. [62] observed that the increased mortality due to encephalomyocarditis virus in CD-1 mice subjected to isolation-induced stress was less obvious in BALB/c mice, a finding that suggests strain-dependent or genetic factors may also be important. The potential contribution of animal age to mortality has not been carefully examined. In all of the studies with rodents, the animals used were 4–8 weeks of age, and those used in studies of primates were adults. The sex of the animals did not appear to influence the results in the few studies in which male and female mice were included [59, 62].

The influence of stress on the pathogenesis of herpes simplex virus has been investigated in murine and bovine models. Stress induced by avoidance learning and restraint increased mortality of mice infected with a herpes simplex virus isolate [59]. In a study reported by Filion et al. [60], stress arising from transportation and handling of 6–8-month-old calves fostered the development of pneumonia and death after challenge with bovine herpesvirus 1. Transported animals had elevated levels of plasma cortisol and a diminished blastogenic response to phytohemagglutinin in vitro. This study supports the long-held belief that stress from transportation plays a role in the development of bovine pneumonic pasteurellosis (shipping or transit fever). In the same study, the transported calves were found to have no greater susceptibility to *Pasteurella haemolytica*, which is capable of causing the disease as a primary pathogen [65]. However, infection with bovine herpesvirus 1 commonly precedes and may increase susceptibility to secondary bacterial infection.

Fluctuating ambient temperature has been evaluated as a naturally occurring stressor in a swine model of viral gastroenteritis [64]. Pigs maintained at an ambient temperature of 30°C remained disease-free after challenge with the virulent coronavirus, a transmissible gastroenteritis-causing virus. However, a sudden drop in temperature to 4°C induced severe diarrhea in virus-challenged pigs. Also, pigs raised at temperatures that fluctuated between 20°C and 4°C developed profuse diarrhea when inoculated with this viral agent.

Forced exercise, which is a complex stressor involving both psychological and physiologic elements, has been used commonly in animal studies of infectious disease outcomes. Forced swimming [53, 54] and exhausting exercise of mice on a treadmill [55] have been associated with increased myocarditis after challenge with coxsackie B3 virus. The timing of initiation of exercise relative to the inoculation of virus appears to be crucial [55]. Although increased mortality of mice infected with the coxsackievirus B3 has been associated with swimming exercise [53], this was not the case in a more recent study in which exercise on a treadmill was used [55]. It is interesting that physical conditioning of mice prior to their inoculation with influenza A abrogated the deleterious effect of swimming exercise that was observed in mice that were unconditioned [61]. In a study of forced exercise, chilling, and mechanical trauma during the incubation period of infection due to poliomyelitis virus in monkeys, Levinson et al. [48] found that the incidence and severity of paralysis was greater in monkeys subjected to exhausting exercise.

Human Studies

Studies of the impact of stress on viral infections in humans have dealt with only a limited number of pathogens (table 3). The effect of physical exertion on the pathogenesis of viral infection in humans was most carefully studied in developed countries during the years of epidemic poliomyelitis. Analy-

Table 3. Stress and viral infections in humans.

Type of infectious disease	Pathogen	Subjects	Stressor	Finding	[Reference]
Poliomyelitis	Poliomyelitis virus	Patients	Physical activity	↑ Paralysis	[66]
Hepatitis	Hepatitis A	Patients	Physical activity	No effect	[67, 68]
Upper respiratory tract infection	Rhinovirus	Prisoners	Cold	No effect	[69]
	Rhinovirus	Volunteers	Life events*	↑ Frequency, severity	[70]
	NAI	Marine recruits	Delayed promotion	↑ Frequency	[71]
	NAI	College students	Life events	↑ Reports of symptoms	[72, 73]
	NAI†	Children	Life events	↑ Duration, severity	[74]
	NAI	Prisoners	Life events	↑ Reports of symptoms	[75]
	NAI†	Adults	Life events	↑ Frequency, duration	[76]
	NAI	Medical students	Exams	↑ Reports of symptoms	[77]
	NAI	Adults	Life events	↑ Reports of symptoms	[78]
Herpes labialis (recurrent)	HSV	Nursing students	Unhappiness	↑ Recurrences	[79, 80]
		Nursing students	Unhappiness	No effect	[81]
Herpes genitalis (recurrent)	HSV	Adults	Life events	No effect	[82]
Infectious mononucleosis	EBV	Cadets	Pressure to achieve academically	↑ Clinical illness	[83]

NOTE. ↑ = increased; NAI = naturally acquired infection; HSV = herpes simplex virus; EBV = Epstein-Barr virus.
* Disruptive or stressful life changes as measured by a variety of standardized questionnaires.
† Cultures were performed for viruses and other potential pathogens.

sis of the data from 411 cases of polio that occurred during three epidemics in the United States revealed that the incidence and severity of paralysis were increased only when physical activity was performed after the second or major phase of illness [66]. Moderate physical exertion during the period of recovery from acute viral hepatitis, on the other hand, has been shown to be nondetrimental [67, 68]. Although there are anecdotal reports of an increased incidence of upper respiratory tract infections in conditioned athletes during periods of exhaustive training [84], no controlled studies have been carried out in this group of subjects. Similarly, no data are available regarding the perceived beneficial effects of moderate exercise regimens on the pathogenesis of the common cold.

In contrast to the paucity of studies on the effects of exercise on the pathogenesis of upper respiratory tract infections, there have been numerous studies of the influence of psychological stressors (disruptive life events) on the course of such infectious disease. A variety of psychometric instruments (e.g., the Life Events Inventory, the Daily Hassles Scale, the Life Changes Inventory, and the Schedule of Recent Experience) have been used to assess stress resulting from disruptive life events, most commonly arising from situations of personal failure, loss of or separation from significant others, or a change in social status. In most studies [71–74] naturally acquired upper respiratory tract infections were evaluated, and data regarding frequency of symptomatic infections were usually obtained from subjects' self-reported information. Virologic confirmation of infection rarely has been attempted in such studies. In addition, although most authors have been aware of potential confounding variables such as sleep deprivation, altered nutrition, use of medications, and alcohol consumption, these factors nonetheless are often difficult to control and to measure accurately.

Despite important shortcomings in most of these studies, the results suggest that stressful life events promote the pathogenesis of upper respiratory tract infections. Supportive data were reported in a study in which volunteers were challenged with rhinoviruses at the MRC Common Cold Research Unit in Salisbury, United Kingdom [70]. Recent life stress significantly increased the magnitude of symptomatic infectious disease in these subjects, although personality traits seemed to be a strong determinant of increased susceptibility in that introverts developed worse symptoms and infections than did extroverts. Results of these viral challenge studies are consistent with earlier observations by Jackson et al. [85], who noted that students who were worried or concerned showed an increased susceptibility to upper respiratory tract infection after challenge with nasal secretions or viruses.

Psychological stressors have been regarded as common triggers of recurrent herpes labialis and herpes genitalis, although this belief has not been documented conclusively. In a series of studies carried out in student nurses, unhappiness (a factor that is measured in the Clyde Mood Scale) was found to be predictive of recurrent herpes labialis in some studies [79, 80] but not in others [81]. In a review of studies of recurrent genital herpes, VanderPlate and Aral [86] concluded that most studies lack proper controls and virologic confirmation of infections. In a recent report, Kemeny et al. [82] found no association between recurrent herpes genitalis and stressful life experiences, although depressive mood and alcohol consumption appeared to increase the risk of recurrences.

In a 4-year prospective study of cadets at the U.S. Military Academy at West Point, N.Y., who were seronegative for Epstein-Barr virus on admission to the study, Kasl et al. [83] found that seroconverters who developed symptomatic infectious mononucleosis had a high level of motivation (desire

to stay in the military), had achieved poor grades for academic performance in the year prior to developing mononucleosis, and were more likely to have fathers who were overachievers. Likewise, Glaser et al. [87] demonstrated that first-year medical students had increased levels of antibody to Epstein-Barr virus, herpes simplex virus, and cytomegalovirus during periods of examination stress. Furthermore, students who had high scores for loneliness on the UCLA Loneliness Scale had the highest titers of antibody to Epstein-Barr virus. Although those investigators did not provide any virologic or clinical correlations to the serologic findings, the results suggest that stress fosters reactivation of herpes viruses [88].

Although these data support the postulate that stress can be a cofactor in the pathogenesis of certain viral infections in humans, a number of limitations can be found in these studies. As has been mentioned, many studies have relied on patients' reports of illness, and since stressed individuals are more likely to seek treatment, the results may have been biased in a positive direction. Furthermore, studies that have yielded negative results may be less likely to be reported. It should also be pointed out that the outcome of infection may be influenced by personality traits and primary emotional disturbances, and these characteristics may be difficult to separate from stress produced by psychological stimuli. For example, obsessional symptoms [89] and a high need for power [90] have been associated with increased frequency or severity of upper respiratory tract infections, and delayed recovery from acute respiratory tract infections and influenza have been associated with various personality disturbances [91–93]. Similarly, personality-related effects on infections caused by herpesviruses have been noted [94–96]. As is the case for studies with animals, the influence of age on the pathogenesis of infection in humans has rarely been evaluated (most studies have been carried out on young to middle-aged individuals), and the potential influence of sex has not been adequately explored. In one large survey, for example, the impact of divorce or separation on acute respiratory tract conditions was observed primarily in women [97].

Bacterial Infections

Animal Studies

It is not surprising that the earliest studies of the effects of stress on the pathogenesis of infectious diseases involved bacterial pathogens. The results of these seminal investigations and of subsequent studies are summarized in table 4. As early as 1890, forced exercise was shown to increase mortality in rats infected with *Bacillus anthracis* [98]. Subsequently, forced exercise in a revolving drum was found to increase mortality due to *Staphylococcus aureus* in rabbits, but this effect was observed only when exercise was initiated at the time of infection [102]. Although exercise before infection with *S. aureus* had no impact on mortality, rabbits were susceptible to *Streptococcus pyogenes* when they were exercised before being inoculated with this organism [102]. In studies with type I *Streptococcus pneumoniae*, forced exercise actually decreased mortality of rabbits when the exercise regimen was begun before bacterial challenge; however, an increased mortality was observed if exercise commenced at the time of inoculation with *S. pneumoniae* [101]. Similarly, mortality was reduced

Table 4. Animal models of stress and bacterial infection.

Bacterial pathogen	Animal	Stressor	Finding	[Reference]
Bacillus anthracis	Rat	Forced exercise	↑ Mortality	[98]
Streptococcus pneumoniae	Rat	Forced exercise	↓ Mortality	[99]
	Guinea pig	Forced exercise	↓ Mortality	[100]
	Rabbit	Forced exercise	↓ or ↑ Mortality	[101]
Streptococcus pyogenes	Rabbit	Forced exercise	↑ Mortality	[102]
Staphylococcus aureus	Rabbit	Forced exercise	↑ Mortality	[102]
	Mouse	Cold	↑ Mortality	[103]
Salmonella typhimurium	Mouse	Cold	↑ Mortality	[103, 104]
	Mouse	Crowding	↑ Mortality	[105]
	Pony	Transportation	↑ Gastroenteritis	[106]
Francisella tularenis	Mouse	Forced exercise	No effect	[61]
	Rat	Forced exercise	No effect	[107]
Lipopolysaccharide of *Escherichia coli*	Swine	Surgery, anesthesia	↑ Mortality	[108]
	Swine	Weaning, transportation	↓ Mortality	[108]
Viridans streptococci, gram-negative bacilli	Opossum	Captivity	Endocarditis, ↑ Mortality	[109]
Mycobacterium tuberculosis	Mouse	Crowding	↓ or ↑ Mortality	[110]
	Mouse, rat	Forced exercise	↑ Mortality	[111]

NOTE. ↑ = increased; ↓ = decreased.

in rats [99] and guinea pigs [100] when exercise preceded *S. pneumoniae* infection. In more recent studies, forced swimming exercise was found to have no effect on the pathogenesis of *Francisella tularensis* infection in mouse [61] and rat [107] models, although this same stressor significantly increased mortality in mice with influenza A [61]. These studies underscore the potential importance of the timing of the stressor and of the virulence factors of specific microorganisms in the determination of the influence of stress on the outcome of infectious disease.

The importance of bacterial virulence in determination of the influence of a stressor on pathogenesis was also observed in studies of mice that were exposed to cold temperatures and challenged with *S. aureus* [103] or *Salmonella typhimurium* [103, 105]. When mice were infected with highly virulent strains of *S. aureus* or *S. typhimurium*, the temperature at which the infected mice were maintained made no difference in the response to infection since all control animals died. However, when relatively avirulent strains were used, increased mortality was noted in mice that were exposed to environmental temperatures of 5°C and 15°C immediately after infection with these strains [103]. In addition, the stress of cold (5°C) markedly increased the susceptibility of mice to the lethal effect of lipopolysaccharide isolated from *Serratia marcescens* [103].

In other studies with *S. typhimurium*, Edwards and Dean [105] found that the stress of crowding (30–60 versus 2–10 animals per cage) increased the mortality of male and female mice inoculated intraperitoneally with this organism. Transportation-induced stress increased the susceptibility of ponies to development of gastroenteritis due to *S. typhimurium* [106], but it is interesting that this stressor appeared to protect piglets from endotoxic shock following intravenous administration of lipopolysaccharide from *Escherichia coli* [108]. Short hauling (12 hours' duration) but not long hauling (24 hours' duration) increased the morbidity and mortality of calves due to respiratory tract infection in cases in which *P. haemolytica* was a common isolate [112], a fact that suggests the calves were able to adapt to this stressor.

Unlike virtually all other animal species, opossums are susceptible to development of bacterial endocarditis without experimental alteration of the heart valve. Opossums taken into zoos or brought into the research laboratory are at risk of spontaneous death due to this infection. Sherwood et al. [109] have provided evidence that suggests stress arising from captivity plays an important role in the pathogenesis of this infection: in an undefined way, stress elicits valvular lesions that are a substrate for infective endocarditis.

Sex-specific influences of stress on outcome of infectious disease were observed in studies by Tobach and Bloch [110], who found that crowding of female mice before or at the time of infection with *Mycobacterium tuberculosis* reduced mortality. In contrast, crowding of male mice resulted in an increased death rate. In another study of experimental stress, forced exercise in a metal wheel or in water (swimming) was associated with increased mortality of rodents infected with *M. tuberculosis* [111].

Human Studies

The possibility that "psychic trauma" might adversely influence the clinical course of human tuberculosis has been suspected clinically for many years [113]. In 1919, a researcher in Japan concluded: "Overtaxation of the mind of our youths by our unsatisfactory educational system seems to be the cause of the high mortality of young consumptives in our country" [114]. Death rates due to tuberculosis and other pulmonary infections in divorced persons have been reported to be greater than those in married individuals [115]. In other surveys, bereavement [116] and "chronic life stress" [117] have been regarded as possible predisposing factors in the development of serious respiratory tract infections such as pneumonia. Stress has also been considered as playing a role in the development of dental caries [118–120], although carefully controlled studies of this postulate are lacking.

In the only longitudinal study of the impact of stress on the pathogenesis of bacterial infection in humans, Meyer and Haggerty [121] found increased acquisition of and illness due to group A streptococci in members of families who experienced a variety of psychological stressors such as loss of a family member, other illness in the family, and divorce. While that study provides suggestive evidence that stress promotes the development of streptococcal pharyngitis, research in the field of bacterial pathogenesis in humans generally has not been as carefully controlled for potentially confounding variables as have studies of viral infections.

Parasitic Infections

Animal Studies

A limited number of studies that deal with the interaction of stress and parasitic infection have been reported (table 5). In a series of experiments using a murine model of malaria, Friedman et al. [122–125] demonstrated that a number of variables modulated the influence of stress on outcome of infectious disease. When housing in groups of five versus housing alone was selected as a stressor, the mice housed in groups had a significantly higher mortality after challenge with *Plasmodium berghei* [122–124]. Although sex of the mice had no effect on outcome, the findings were clearly dependent on mouse strain. While increased mortality was consistently observed in mice of the CD-1 strain, no effect was seen in mice of five other strains [124]. Stress induced by avoidance learning had the opposite effect of that induced by type of housing; i.e., mortality was reduced by subjecting mice to electric shock preceded by a warning light. However, avoidance learning promoted the lethality of coxsackie virus B-2 in the same model [123].

Table 5. Animal models of stress and parasitic infection.

Parasite	Animal	Stressor	Finding	[Reference]
Plasmodium berghei	Mouse	Housing in groups	↑ Mortality	[122–124]
	Mouse	Avoidance learning	↓ Mortality	[123, 125]
Hymenolepsis nana	Mouse	Social	↑ Reinfection	[126]
	Mouse	Cat	↑ Reinfection	[127]
Entamoeba species	Squirrel	Cold	↑ Cecal organisms	[128]
Trypanosoma cruzi	Mouse	Forced exercise	↑ Mortality, myocarditis	[129]
Toxoplasma gondii	Rat	Cold, heat	↑ Lung disease	[130]
	Mouse	Restraint	↑ Mortality	[131]

NOTE. ↑ = increased; ↓ = decreased.

Two studies of murine gastrointestinal infection due to the dwarf tapeworm *Hymenolepsis nana* have been reported, both of which used more naturally occurring stressors. Social stress (association with strange mice and severe fighting) of animals with acquired immunity to this parasite resulted in reinfection [126]. This effect was limited to mice with a low social status and was not observed in dominant males. An increased reinfection rate was also observed when predator (cat)–induced stress was used; in this study, adrenal hypertrophy and increased serum corticosteroid levels were used as markers of stress [127]. In a similar study, a cold environment was used as a natural stressor in ground squirrels. An increased number of naturally acquired *Entamoeba* organisms was found in the gastrointestinal tracts of cold-exposed animals [128]. Extremes of ambient temperature (10°C or 35°C) have been shown to promote pulmonary pathology in rats during acute infection with the RH strain of *Toxoplasma gondii* [130].

In a study in which forced swimming exercise was used as a stressor, Elson and Abelmann [129] demonstrated more-severe myocarditis and increased mortality in mice infected with *Trypanosoma cruzi*. Chao et al [131] recently reported that restraint-induced stress in BALB/c mice promoted the lethality of infection due to *T. gondii* C56, a virulent strain of this protozoan. However, those investigators were unable to detect any adverse effect of this stressor in mice inoculated with *T. gondii* Me49, a relatively avirulent strain. Thus, the strain of both the host and the pathogen appear to affect pathogenesis of infection.

Conclusions

A large body of evidence that has emerged in the past decade indicates that exposure to a variety of psychological, environmental, and physiologic stressors can result in alterations of immune cell functions [14–19]. Most studies have demonstrated that stress is associated with suppressed host-defense mechanisms, although in some instances enhanced immune reactivity has been observed. Similarly, the results of a majority of studies related to pathogenesis of infectious disease suggested that stress interferes with host defense. However, in a distinct minority of cases, stress appeared to enhance host survival. Few studies have identified the mechanism(s) responsible for stress-induced alterations of microbial pathogenesis, although stress-responsive neuropeptides and catecholamines [132–133] have been implicated.

Although the accumulated data support the hypothesis that stress alters the pathogenesis of infectious disease, substantial limitations have existed in many of the studies with humans and in the animal models. To date, only a small number of viral and bacterial infections have been investigated in both human subjects and animal models. Studies of parasitic infections have been restricted to murine species, and no meaningful reports relating effects of stress on the outcome of fungal disease could be found. Of the variables that are known to influence the outcome of a host-parasite interaction, many have been shown to alter the impact of stress on the pathogenesis of infection; these factors include the microbial species and strain as well as the sex and immune status of the host and the type, timing, and duration of the stressor, relative to the onset of infection (figure 2). The potential importance of some variables, e.g., extremes of age, poor nutritional status, and the presence of concomitant diseases, has not yet been investigated. Given the well-known contribution of these factors to microbial pathogenesis, their influence should be explored. In addition, more studies need to be designed to analyze the potential interaction between the external stressor and personality, since the latter may determine the somatic response to the stressor.

The major advances witnessed in research of microbial pathogenesis coupled with the progress seen in the field of psychoneuroimmunology in recent years should permit greater insight into the cellular and molecular basis of stress-induced influences on the outcome of infectious diseases. Now that it has become abundantly clear that the brain and immune system communicate, it is time for more active interchange between those most familiar with the complexities of the brain—neuroscientists, psychiatrists, psychologists—and investigators of infectious diseases. Because human studies are fraught with variables that are difficult to control, e.g., nutritional factors and the use of medications or substances that might alter host defenses, animal models remain essential. Mounting concerns regarding the ethics of animal experimen-

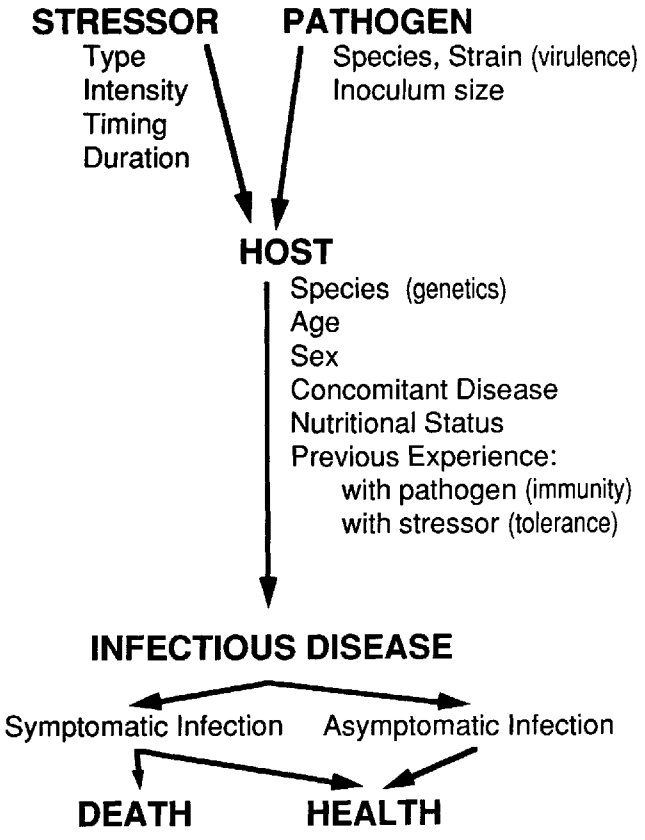

Figure 2. Various factors can modify the impact of a stressor on the pathogenesis of an infectious disease.

tation, however, support the need for greater use of naturally occurring stressors in such research, as well as the use of pathogenic endpoints other than mortality. Since stress appears to have an adverse impact on livestock by promoting the development of infections, these animals represent a particularly relevant model for investigation. Stress-associated immune suppression has been considered as a potential cofactor in the pathogenesis of human immunodeficiency virus infection [134]. Given increased research funding for all aspects of the acquired immunodeficiency syndrome, this is an area of human medicine that is likely to receive increased attention. The question regarding whether stress plays a role in the pathogenesis of postsurgical infections or other types of nosocomial infections might also prove worthy of investigation; certainly, the hospital is a stressful environment [135].

The fact that the human condition is characterized by stress—yet illness due to infectious disease is a relatively rare occurrence in healthy individuals—suggests that successful coping mechanisms are the rule. As pointed out by Hans Selye over 30 years ago, new approaches to prevention and therapy of infectious disease may come from increased understanding of these mechanisms: "If I may venture a prediction, I would like to reiterate my opinion that research on stress will be most fruitful if it is guided by the principle that we must learn to imitate—and if necessary to correct and complement—the body's own autopharmacologic efforts to combat the stress factor in disease" [136].

Acknowledgment

The authors thank Dr. Bruce Overmier for his insights and Ms. Beth Olson for her expert secretarial assistance.

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