Psychological Bulletin
1991, Vol. 109, No. 1, 5-24

0033-2909/91/$3.00

Stress and Infectious Disease in Humans

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This article reviews research on the role of stress in infectious disease as measured either by illness behaviors (symptoms and use of health services) or by verified pathology. Substantial evidence was found for an association between stress and increased illness behavior, and less convincing but provocative evidence was found for a similar association between stress and infectious pathology. Introverts, isolates, and persons lacking social skills may also be at increased risk for both illness behaviors and pathology. Psychobiological models of how stress could influence the onset and progression of infectious disease and a psychological model of how stress could influence illness behaviors are proposed.

Psychologists interested in the role of psychological factors in human diseases have focused primarily on coronary heart disease and cancer to the relative neglect of infectious diseases. For example, the role of stress and other psychological factors in infectious disease is not a topic in *Behavioral Health*, Matarazzo, Weiss, Herd, Miller, and Weiss' (1984) compendium of the field nor in either of the *Annual Review of Psychology* chapters on Health Psychology (Krantz, Grunberg, & Baum, 1985; Rodin & Salovey, 1989). However, interest in this area has been recently stimulated both by evidence that psychological factors influence immune function (e.g., Ader, 1981; Coe & Levine, in press; Jemmott & Locke, 1984) and by increasing recognition of the importance of understanding the role of stress and other psychological factors in the onset and progression of acquired immunodeficiency syndrome (AIDS; Baum & Nesselhof, 1988; Kiecolt-Glaser & Glaser, 1988b).

When exposed to an infectious agent, only a proportion of people develop clinical disease (Cornfeld & Hubbard, 1964; Fernald, Collier, & Clyde, 1975). Moreover, severity and duration of symptomatology vary widely among those who do become ill. Reasons for variability in response are not well understood and the possibility that psychological factors play a role has received increased attention (e.g., Bierman, 1983; Stein, 1981). The purpose of this article is to address the possible role of psychological factors in the etiology and progression of infectious diseases. Because the majority of studies in this literature examine the influence of *stress* on susceptibility, our review and theoretical discussion focus on stress. However, in reviewing the literature, we also touch on other psychological factors that have been investigated as risk factors for infection.

We begin by providing background information on psychological and biological issues involved in studying the relation between stress and infectious disease. We then propose models of how stress could influence infectious pathology and how stress could influence illness behaviors; address methodological and conceptual problems relevant to designing and conducting studies in this area; and review and interpret the literature on psychological influences on the onset, duration, and recurrence of infections in humans.

Definitions

What Do We Mean By Stress?

The focus of this article (and of the work we review) is on negative stressful life events and negative affective states as possible contributors to the development of infectious pathology. The theoretical models we propose assume that negative events (major or daily) and psychological distress measures tap different stages of the same underlying process: stressful events, causing negative affective states that (for reasons described later) put people at higher risk for infectious disease. We recognize that negative events do not always trigger psychological distress. Distress arises only when imposed demands are perceived to exceed ability to cope (Lazarus & Folkman, 1984). However, the work we review does not address conditions under which environmental stressors produce distress. Moreover, categorizing studies according to whether they use stressor or distress measures does not predict study results. As a consequence, our theoretical discussions begin with stressor-elicited distress. We caution the reader, however, that there are important psychological moderators of the stressor–distress relation (see reviews by Cohen & Edwards, 1989; Cohen & Wills, 1985; Gentry & Kobasa, 1984; Kessler & McLeod, 1985).

For the most part, the stressor and distress measures used in

Sheldon Cohen's participation in the preparation of this article was supported by a Research Scientist Development Award from the National Institute of Mental Health (K02 MH00721) and grants from the National Institute of Allergies and Infectious Diseases (AI23072) and the Office of Naval Research (N00014-87-K-0369). Gail M. Williamson's participation was supported by a postdoctoral fellowship in Clinical Services Research from the National Institute of Mental Health (MH17184) and by a grant from the National Institute on Aging (R. Schulz, principal investigator, AG0-5444). We thank Joan Cunnick, Robyn Dawes, Bruce Rabin, Richard Schulz, and David Tyrrell for their comments on an earlier draft.

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this literature are cumulative; that is, they combine events or assess general (source unspecified) distress. Many of the studies use major stressful life event or daily event checklists. Examples of events included in major life event checklists are moving, divorce, and death of a loved one. Major stressful life event measures used in the reviewed literature include versions of Holmes and Rahe's (1967; Holmes & Masuda, 1974) original scale (e.g., Schedule of Recent Life Experience [SRE], Social Readjustment Rating Scale [SRRS], and Life Change Inventory [LCI]) as well as several second generation scales (e.g., Life Events Survey [LES], Sarason, Johnson, & Siegel, 1978; College Student Life Events Scale [CSLES], Levine & Perkins, 1980; Life Events Inventory [LEI], Tennant & Andrews, 1976; and Psychiatric Epidemiology Research Interview [PERI], Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978). Examples of events in daily event checklist include misplacing or losing things, social obligations, and problems and arguments with friends. Daily event measures used in the reviewed literature include the Daily Hassle Scale (DHS; Kanner, Coyne, Schaeffer, & Lazarus, 1981) and the Assessment of Daily Experience (ADE; Stone & Neale, 1982). Finally, psychological distress measures include items (and subscales) assessing anxiety, depression, dysphoria, and other negative affective states—all highly intercorrelated components of distress (Dohrenwend, Shrout, Egri, & Mendelsohn, 1980). Distress measures used in the reviewed literature include the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erlbaugh, 1961), Cornell Medical Index (CMI; Brodman, Erdman, & Wolff, 1956), General Health Questionnaire (GHQ; Goldberg, 1972), Manifest Affect Rating Scale (MARS; Spilken & Jacobs, 1971), Middlesex Hospital Questionnaire (MHQ; Crown & Crisp, 1966), Minnesota Multiphasic Personality Inventory (MMPI; Hathaway & McKinley, 1951), Mood Adjective Checklist (MACL; Nowlis, 1965), and Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971). (Abbreviations used in the text for each of the stressor and distress scales are provided in Table 1.) We recognize that scores on cumulative events and psychological distress measures may be partly or wholly attributable to trait (as opposed to state) distress and address this issue in the Discussion section.

Table 1
Abbreviations for Stressor and Distress Measures

Abbreviation	Measure
	Major life events scales
CSLES	College Student Life Events Scale
SRE	Schedule for Recent Life Experience
SRRS	Social Readjustment Rating Scale
LCI	Life Change Inventory
LES	Life Events Survey
LEI	Life Events Inventory
PERI	Psychiatric Epidemiology Research Interview
	Daily life event scales
ADE	Assessment of Daily Experience
DHS	Daily Hassle Scale
	Psychological distress scales
BPI	Boston University Personality Inventory
BDI	Beck Depression Inventory
CMI	Cornell Medical Index
GHQ	General Health Questionnaire
MACL	Mood Adjective Checklist
MARS	Manifest Affect Rating Scale
MHQ	Middlesex Hospital Questionnaire
MMPI	Minnesota Multiphasic Personality Inventory
POMS	Profile of Mood States

What Do We Mean By Infectious Disease?

Infectious diseases result from the growth and action of microorganisms or parasites in the body and may or may not be contagious. The diseases studied in the literature we review include those believed to be caused by viruses, bacteria, and mycoplasma. Standard research criteria for diagnosis of *clinical* infectious disease require *both* biologic evidence of infection and manifestation of related symptomatology (Beare & Reed, 1977; Kasl, Evans, & Neiderman, 1979). Below, we discuss measures of infection and symptomatology, as well as indirect measures sometimes used as disease markers.

Infection

Biological verification of infection can be accomplished by establishing that an infectious agent is present or replicating in tissue, fluid, or both. Studies of diseases with unknown etiologies, for example, community studies of upper respiratory infections (URI), often use generic methods for detecting the presence of *unspecified* pathogens. A common procedure is to culture the sample (put it in a medium that stimulates pathogen reproduction). If pathogens are present they will reproduce in the medium and can be detected with the naked eye or under magnification. This procedure works well for detecting unspecified bacteria but not for viruses.

Studies of diseases with known etiologies, for example, viral inoculation studies, use methods designed to detect the presence of a particular pathogen. This can be done by (a) culturing samples in mediums that stimulate growth of only certain pathogens or (b) demonstrating that the immune system is responding to an agent by producing antibodies. Antibodies are protein molecules that attach themselves to invading microorganisms and mark them for destruction or prevent them from infecting cells. Because each antibody recognizes only a single type of microorganism, the production of antibodies to a specific infectious agent is evidence for the presence and activity of *that* agent. Antibody levels are generally assessed by determining the extent to which the serum from an infected person binds to a sample of an infectious agent. A significant increase (within subject) in the level of antibodies to a specific agent is considered evidence for infection by that agent (see techniques for determining significant within-individual increases described in Ershler, Moore, & Socinski, 1984).

We have suggested that the presence of an infectious agent can be established either directly through the use of culturing techniques or indirectly through detection of significant increases in antibodies to that agent. These two techniques, however, are often only moderately correlated and optimally, both

procedures should be included to verify infection (Beare & Reed, 1977). Either antibody increase *or* detection of the pathogen is considered sufficient evidence of infection.

Procedures for detecting pathogens and their antibodies are invasive, time consuming, and expensive. Moreover, in naturalistic studies, techniques for screening symptomatic patients to verify diseases caused by unknown pathogens are not especially successful in finding responsible agents (e.g., 28% verification in Boyce et al., 1977; 15% verification in Graham, Douglas, & Ryan, 1986).

Signs and Symptoms

Measures of disease symptomatology in this literature can be separated into two categories: signs and symptoms. *Signs* are observable (sometimes with the aid of x-rays or other technology), for example, lesions, rashes, and swelling. Trained clinicians are often used to identify observable signs such as the occurrence of oral lesions in herpes simplex. *Symptoms* are *not* observable but are reported by a patient, for example, headaches and stomachaches. Although it is theoretically possible to validate symptom protocols by establishing that they are strongly associated with verified disease outcomes, there is only one study in this literature (Friedmann, Katcher, & Brightman, 1977) that reports such a validation.

Many of the studies use unverified self-reported symptom protocols as their only criterion for disease. Although these reports may reflect underlying infectious pathology, they may also reflect influences of stress on cognitive processes and self-perceptions that are *not* associated with infectious disease. In other words, people may report symptoms or illness episodes without actually experiencing clinical illness or may not report symptoms or illness episodes when they do have clinical disease. Nonpathogenic pathways that might link stress to symptom reporting are discussed later.

Seeking Medical Care

A final measure of illness used in this literature is use of health-care services. Seeking medical care involves both defining a constellation of symptoms as an illness and deciding to seek care. As with self-reported symptoms, multiple psychological processes are involved. Such behavior may be driven by underlying infectious pathology but may often occur independent of pathology. Moreover, those seeking care who actually have verifiable pathology are not necessarily representative of persons with that disease. In short, those who do not seek care may be as ill as those who do, and these groups may differ psychologically.

How Could Stressors Influence Infection and Illness?

Stressors are generally thought to influence the pathogenesis of physical disease by causing negative affective states (such as anxiety and depression), which in turn exert direct effects on biological processes or behavioral patterns that increase disease risk (see Cohen, Evans, Stokols, & Krantz, 1986; Krantz, Glass, Contrada, & Miller, 1981). We recognize that stressors may also elicit behavioral or biological changes that *decrease* disease risk. Although our models primarily address the former hypotheses, we discuss stressor-induced health promoting pathways as well. The focus of this article is on negative stressful life events and negative affective states as possible contributors to pathology. Our models start with negative affective states and do not address the conditions under which environmental stressors produce negative affect (see Lazarus & Folkman, 1984, for discussions of these issues). In our theoretical discussion, we use the term *stress* because we are discussing the state of psychological distress and not environmental characteristics (*stressors*) that may contribute to that state.

Even the most severe stress cannot result in infection without the presence of an infectious agent. Plausible routes through which stress might influence susceptibility to infectious disease include (a) altering biologic susceptibility and hence *predisposing* persons exposed to a pathogen to infection, (b) *initiating* or triggering a process that allows a pathogen that is already in the body (e.g., a latent virus) to reproduce, or (c) contributing to *maintenance* of an ongoing pathogenic process.

We propose two models representing plausible pathways linking stress to infectious pathology. The first addresses the role of stress in predisposing persons to the onset of a new infection. The second model addresses pathways through which stress may influence duration and severity of an existing infection either by maintaining ongoing pathogenic processes or by initiating (reactivating) latent infections. Pathways in each of these models are depicted in Figures 1 and 2, respectively, and are described later.

We also propose a third model addressing how stress may influence labeling of physical sensations as symptoms, labeling of symptoms as disease, and use of health care facilities. Our intent is to provide explanations for stress-induced illness behaviors that do not assume underlying pathology. This model is depicted in Figure 3. All three models indicate paths moving in only one causal direction, from stress to disease or from stress to illness behaviors. Alternative paths are excluded for the sake of brevity. Their exclusion is not intended to reflect hypotheses about their existence.

Stress and the Onset of Infectious Disease

Susceptibility to infection is presumed to be primarily mediated by immune function. As indicated in Figure 1, stress may influence immunity either through direct innervation of the central nervous system (CNS) and immune system (nerves terminating in lymphoid organs), or through neuroendocrine-immune pathways (release of hormones). A number of direct neural pathways linking the CNS to the immune system have been identified (e.g., Felten, Felten, Carlson, Olschowka, & Livnat, 1985; Felten & Olschowka, 1987). In the case of hormonal pathways, a wide range of hormones released under stress have been implicated in immune modulation. Examples include the catecholamines epinephrine and norepinephrine secreted by the adrenal medulla, cortisol secreted by the adrenal cortex, growth hormone and prolactin secreted by pituitary gland, and the natural opiates beta endorphin and enkephalin released in the brain (see Baum, Grunberg, & Singer, 1982, for discussion of hormones released under stress; see Hall & Goldstein, 1981; Laudenslager, 1988; Rabin, Cohen, Ganguli, Lysle, & Cunnick,

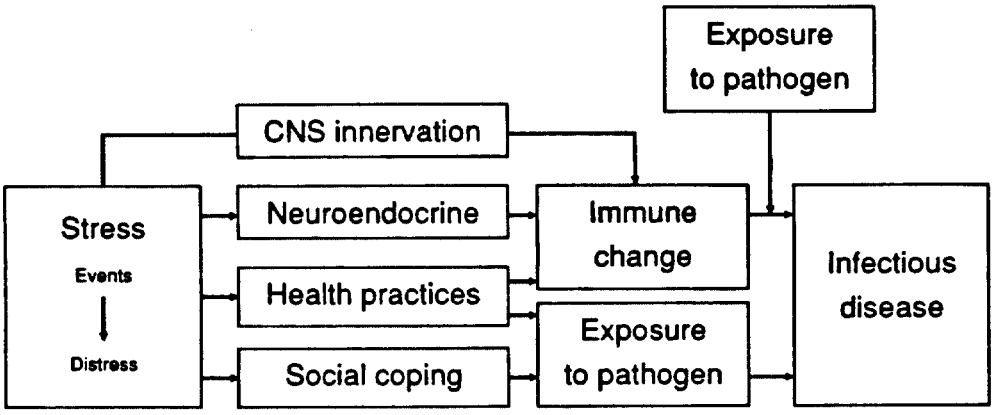

Figure 1. Behavioral and biological pathways linking stress to the onset of infectious diseases. (CNS = central nervous system. For brevity, the model indicates paths moving in only one causal direction, from stress to disease.)

1989, for discussions of the influence of these hormones on immune function).

Behavioral changes occurring as adaptations or coping responses to stress may also influence immunity. For example, persons under stress tend to engage in poor health practices. They may smoke more, drink more alcohol, eat poorly, and sleep less (Cohen & Williamson, 1988; Conway, Vickers, Ward, & Rahe, 1981). Increased smoking, drinking, and changes in diet may all influence immune response (see Kiecolt-Glaser & Glaser, 1988a).

Although effects of stress on immune response are often described as immunosuppressive, implications of stress-induced immune changes for disease susceptibility are not as yet clear. First, in studies of stress effects on immunity, immune responses of stressed persons generally fall within *normal* ranges (Laudenslager, 1987; Rabin et al., 1989). Second, there are few data on immune status in healthy persons as a predictor of disease susceptibility. There is sufficient evidence to convince us that stress influences the immune system. However, it is not clear that either the nature or magnitude of change found in these studies alters disease susceptibility (Calabrese, Kling, & Gold, 1987; Jemmott & Locke, 1984; Palmblad, 1981). Finally, the immune system is complex: One or even several measures of immune function may not provide an adequate representation of host resistance (Palmblad, 1981; Plaut & Friedman, 1981; Rogers, Dubey, & Reich, 1979).

Behavioral changes under stress may also influence susceptibility to infection by influencing whether and for how long persons are exposed to pathogenic agents. For example, stressed persons often engage in *social coping*—drawing on the resources of their social networks (Cohen & Wills, 1985). Increased interaction with others results in greater probability of exposure to infectious agents and consequent infection. However, social interaction under stress is, to some degree, influenced by both the nature of the stressor (Cohen & McKay, 1984) and individual differences in social skills and affiliative

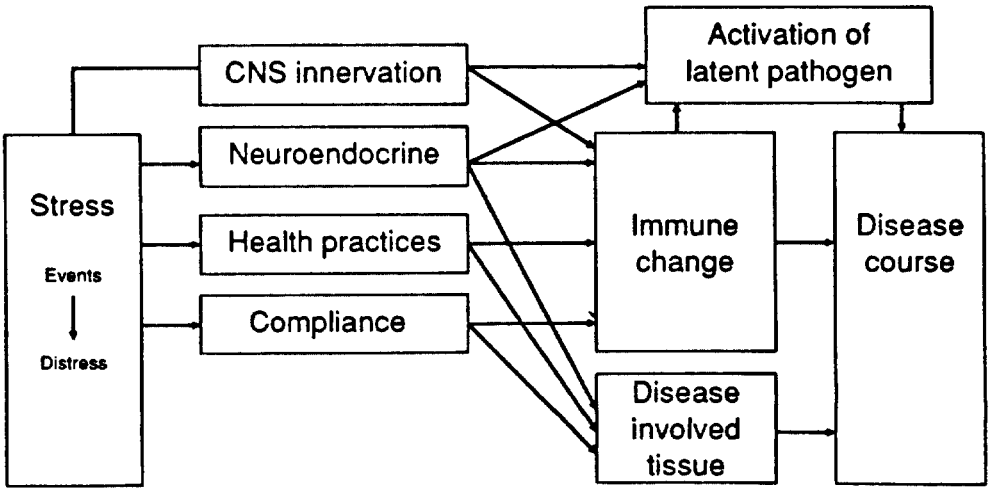

Figure 2. Behavioral and biological pathways linking stress to reactivation of latent pathogens and to the severity of infectious disease. (CNS = central nervous system. For brevity, the model indicates paths moving in only one causal direction, from stress to disease.)

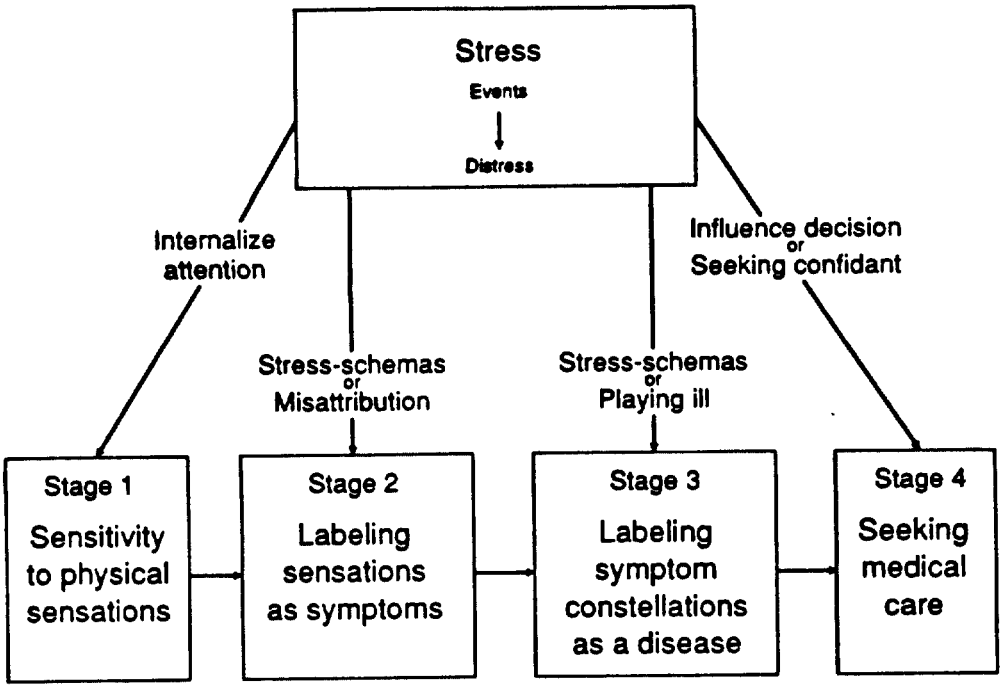

Figure 3. Psychological pathways linking stress to illness behaviors. (For brevity, the model indicates paths moving in only one causal direction from stress to illness behavior.)

tendencies (Heller, 1979). Hence, under some conditions stress may lead to social withdrawal and decreased risk of exposure. Other stress elicited behaviors, for example, unsafe sexual practices or poor hygienic practices, could also increase exposure to infectious agents.

Stress and the Severity and Course of Infectious Disease

Pathways proposed as responsible for changing immune function and hence predisposing persons to disease onset (Figure 1) are also involved in modeling stress effects on duration and severity of disease (Figure 2). However, the course of illness may be influenced by direct effects (not involving the immune system) on *disease-involved tissues* as well. For example, stress-triggered hormones such as cortisol and epinephrine may increase mucous secretion and vasodialation (Laudenslager, 1987) or modulate reflex responses enhancing symptoms such as irritation or sneezing. Stress may also influence disease-involved tissue through changes in *health practices.* For example, increased smoking under stress could irritate nasal and lung tissues. Finally, failure to *comply* with medical regimens under stress could result in more severe and longer-lasting illness, either because undesirable behaviors aggravate existing problems or because failure to perform desirable behaviors (e.g., following medication regimens) results in disease progression. These actions may occur through influences on immune function or through influences of disease-involved tissue.

As indicated in Figure 2, stress may also play a role in reactivating latent pathogens (agents already in the body but not currently multiplying). Diseases with latent viral states include oral and genital herpes as well as AIDS. Reactivation could occur through hormonal or neural stimulation of pathogen reproduction or through suppression of aspects of the immune system that might otherwise hold the pathogen in check (Glaser & Gotlieb-Stematsky, 1982; Kiecolt-Glaser & Glaser, 1987a).

Stress and Illness Behaviors

Our final model addresses how stress may influence the various stages of recognizing and acting on symptoms. Illness behaviors are often accurate indicators of underlying pathology. However, stress and other psychological factors can independently influence these behaviors. This model presents explanations for how stress may influence symptom reporting and medical care seeking without influencing pathology. These mechanisms may operate alone or in conjunction with stress-induced pathology to influence illness behaviors.

Figure 3 depicts the potential sequence of processes that might lead from physical sensation to seeking medical care: sensitivity to physical sensations, labeling sensations as symptoms, labeling symptom constellations as disease, and seeking medical care. These processes are discussed in detail by others (see Cacioppo, Andersen, Turnquist, & Tassinary, 1989; Leventhal, Meyer, & Nerenz, 1980; Mechanic, 1972; Pennebaker, 1982). Although we recognize that there are multiple cultural, social, and individual determinants of illness behaviors, our model only addresses how each behavior may be influenced by stress.

Because psychological stress often triggers physiologic arousal, people under stress may be more attentive to their internal physical states (Stage 1). Stress may also facilitate the labeling of sensations as symptoms (Stage 2) because people are

reminded (in cognitive parlance, a schema is triggered) of previous times when stress was associated with symptoms or simply because they believe that stress triggers symptoms. Alternatively, stress may result in physical sensations whose causes are mistakenly attributed to disease symptoms rather than the stress (Mechanic, 1972; Schachter & Singer, 1962). Labeling symptom constellations as disease may similarly be activated by stress–disease schemas (Stage 3). For example, it is widely believed that stress causes the recurrence of oral herpes. Under stress, a minor oral lesion that would be ignored under nonstressful conditions may be defined as disease recurrence. Reports of symptoms and illness are also ways to avoid stressful situations (Mechanic, 1977). The prototypic example is the child who reports symptoms to avoid attending school on an especially stressful day (playing ill). Finally, stress may influence the decision to seek medical care when persons label themselves as ill (Stage 4). Stress could interfere with deciding whether it is necessary to seek care, increasing care seeking for minor symptoms or decreasing care seeking for serious ones. Persons under stress may also seek medical care unnecessarily because medical providers are viewed as persons to whom one can confide problems. Stress could also *decrease* care seeking because the time demands of many stressors make such visits inconvenient (Schulz, Visintainer, & Williamson, 1990).

Stress-triggered illness behaviors are thought to be general in nature, that is, they do not fall within the domain of a single disease (Pennebaker, 1982; Rabkin & Struening, 1976; Spilken & Jacobs, 1971). Therefore, to the extent that stress effects on illness behaviors are *not* disease specific, there is reason to assume that they are caused by psychological processes influencing symptom reporting and care seeking rather than by underlying pathology.

We have proposed plausible psychological and biological pathways that could link stress to disease. Unfortunately, existing research has focused on establishing a relation between stress and infectious disease with only a handful of studies assessing possible pathways through which such an association might occur. These models provide psychological and biological reasons for expecting stress to increase risk for infectious disease and theoretical frameworks for future work.

Methodological Approaches

Of the many published papers addressing the role of psychological factors in infectious disease in humans, relatively few meet contemporary scientific criteria. Our review is limited to published studies (as of August, 1989) that use standardized measurement, include control groups, and use procedures allowing statistical inference. We have excluded anecdoctal accounts of patients' experiences, descriptions of clinical cases, and speculative pieces by physicians who notice similarities among their patients. We have also excluded work not published in peer review journals and secondary descriptions of unpublished work.

Causal Inference

The human literature relating stress to infectious disease is limited to *correlations* between stress and disease. In a typical study, persons reporting high stress are compared to those reporting relatively lower levels of stress in terms of their risk for developing disease. Although a correlation between stress and disease suggests that stress makes people vulnerable to infectious agents, it may also be that disease (or premorbid pathology) causes greater stress, or that a third factor (e.g., age or social class) puts people at higher risk for both stress and disease. We review relevant retrospective studies. However, we place special emphasis on prospective studies where subsequent disease is predicted from stress levels in *initially healthy* persons. In prospective studies, the possibility that disease-caused stress can be eliminated (see discussions in Cohen et al., 1986, chap. 2; Kessler, 1983; Monroe, 1983). Several prospective studies are infectious-challenge trials in which healthy volunteers were experimentally exposed to a specific infectious agent after psychological measures were taken. Infection and (in most cases) symptoms were then assessed over a period of several days. This design eliminates stress influences on exposure to an infectious agent as an explanation for relations between stress and infectious outcomes.

Rates of Infectious Disease

To predict the occurrence of a disease in a sample, a reasonable percentage of the sample must develop the disease over the course of a study. Although the minimum percentage infected depends on sample size, in the relatively small samples (less than 300) typically used in the verified disease studies in this literature, an infection rate of at least 25% is usually required. This is one reason why the infectious diseases studied most often in this literature are colds, influenza, and herpes—diseases with very high base rates of occurrence.

Other Factors Influencing Susceptibility to Infection

Stress is not the primary etiologic agent in infectious disease, but rather, may be one of many contributors. The primary factor in susceptibility is prior exposure and consequent development of immunity. This immunity is partly attributable to the production of antibodies that occurs when persons are exposed to an infectious agent. Some antibodies remain in circulation and help fight the same infectious agent upon later exposure. Presence of antibodies also provides evidence of prior exposure. Exposure to an infectious agent also sensitizes a population of white blood cells (lymphocytes) to recognize and aid in destroying that agent upon subsequent exposure.

Other factors influence risk for infectious disease (see Jackson et al., 1960; Jemmott & Locke, 1984; Kiecolt-Glaser & Glaser, 1988a; Plaut & Friedman, 1981). These include nutritional status of the host, previous history of illness, presence of other disease, genetic–immune factors, age, race, gender, pregnancy, rhythms (e.g., circadian, menstrual phase, annual), and seasons of the year (e.g., temperature, light exposure). Some of these factors (e.g., race and gender) may be correlated with both stress and infection and consequently provide alternative (spurious) explanations for correlations between stress and infectious disease. Each factor may also make significant independent contributions to unexplained error variance. The more of these factors controlled for in any study, the greater the probability of

isolating effects of stress in the context of multiple environmental, social, and biological predictors (see Plaut & Friedman, 1981; Schleifer, Scott, Stein, & Keller, 1986).

Review

As discussed earlier, a conservative research criterion for diagnosis of clinical infectious disease requires both biologic evidence of infection and manifestation of related symptomatology. Because of the relatively small number of studies using this criterion, we take a somewhat less conservative approach. We treat studies using symptoms *in addition to* biologically verified infection as well as those using physician diagnosis as studies of verified disease.

A number of the investigations, especially those of unidentified URI, include *only* illness behavior measures. In our review, we include only those illness behavior studies intended to identify behaviors specifically associated with an infectious disease, in most cases URI.

Also of concern is the differentiation between subclinical and clinical infection. In short, persons can be biologically infected without manifesting symptoms. It is not known whether this occurs because the biologic response is not sufficient to result in symptoms or because the immune pathways involved in subclinical and clinical responses are different. For the most part (an exception is made in *Herpesvirus Infections*), we review studies with biologic verification but without symptom measures in the verified disease section. However, we caution that there are great practical and theoretical differences between subclinical and clinical disease. Biologic response alone (e.g., increased antibody response) is *not* sufficient evidence for clinical disease.

Our review is organized into separate sections on human studies of (a) upper respiratory infections, (b) herpes infections, and (c) miscellaneous bacterial infections. This categorization has no inherent biologic basis, but rather reflects areas in which work has been done. Most URI studies either combine viral and bacterial infections or address unidentified infections. Hence, we review all URI studies in one section rather than separate the few that were specifically viral or bacterial. We do not review infrahuman studies (see reviews by Monjan, 1981; Plaut & Friedman, 1981; Rogers et al., 1979), although we do draw on the animal literature to both clarify and raise issues.

In each section, we distinguish between retrospective and prospective studies. When relevant, prospective infectious-challenge studies—in which volunteers are experimentally exposed to an infectious agent—are also treated separately. Evidence relevant to neuroendocrine, immune, and behavioral pathways (as proposed in our models) is addressed in *Testing Pathways*, at the end of the review.

Upper Respiratory Infection

The respiratory system is vulnerable to a wide range of viral and bacterial infections. Most familiar are common colds and influenza. Colds and flu are both viral infections. Colds can be caused by more than 100 viruses. Influenza is primarily caused by two types of viruses (A and B), each with many subtypes and strains, but influenza-type diseases can also be caused by many other viruses, for example, adenoviruses, parainfluenza, and respiratory syncytial virus. Both colds and flu are characterized by sore throat, congestion, and mucus secretion. Unlike most colds, however, flu can be accompanied by elevated temperature, gastrointestinal discomfort, and joint pain. Viral infections of the upper respiratory tract are sometimes complicated by secondary bacterial infections caused by inflammation of mucous membranes reducing ability to protect against pathogenic bacteria.

Illness Behaviors

We begin by discussing work on associations between psychological factors and illness behaviors. In these studies, outcomes include URI symptoms, health care utilization, or both, without medical or biologic verification of disease.

Retrospective studies. Several retrospective studies report relations between psychological distress measures and URI-related illness behaviors. Self-reported incidence of URI has been associated with high self-rated negative impact of life events (LES) and high scores on the Taylor Manifest Anxiety Scale, a measure of trait anxiety (Belfer, Shader, Mascio, Harmatz, & Nahum, 1968). High numbers of stresses (upsets, worries, sources of tension, etc.) have also been associated with retrospective reports of URI severity as well as severity of all illnesses (McClelland, Alexander, & Marks, 1982). In one study, use of health services was similarly higher among those reporting more life changes (LCI)—especially personal failures (Jacobs, Spilken, Norman, & Anderson, 1970).

These studies also include failures to find associations between measures of both trait anxiety (Scheier Cattell Anxiety Battery) and depression (Depression scale of the MMPI) and retrospective reports of URI episodes (Belfer et al., 1968) and between life event impact (LES) and use of health services (Sarason, Sarason, Potter, & Antoni, 1985). Other psychological measures not associated with illness behaviors include power motivation (McClelland et al., 1982; McClelland, Floor, Davidson, & Saron, 1980) and perceived social support (Sarason et al., 1985).

Stress may also interact with other psychological variables in predicting URI symptomatology. For example, Sarason et al. (1985) found that those with many negative life events *and* few social supports were more likely to report chronic (mostly URI) illness than all other groups. McClelland et al. (1982) found that people that were *both* high in number of stresses and in need for power reported more severe illness than all other groups combined. In a similar study, McClelland et al. (1980) found that persons with high numbers of stressful life events (SRRS), need for power, *and* action inhibition reported more illnesses, more severe URIs, and more severe non-URI illnesses.

Prospective studies. Parens, McConville, and Kaplan (1966) tracked the use of health services of two samples of first year nursing students (Ns = 75 and 61) for 8 months after administering a series of psychological measures. In both studies, those reporting poor adjustment to their new environment (on a measure devised by the authors) and those reporting very high depressive affect (BDI) used health services (mostly for URI) more frequently. In the second study only, a positive relation was

found between life events (object losses over the entire life) and illness frequency. Number of health service visits was also higher among those with the highest scores on a helplessness ("giving up") measure devised by the authors.

Spilken and Jacobs (1971) administered a series of psychological scales—LCI, MARS, and BPI (Boston University Personality Inventory)—to 92 healthy college students and then monitored them for a year. Those seeking medical care for URI during the year had reported more life events and negative affect and had higher scores on trait measures of defiance and neurotic emotionality. Those reporting having sought care for non-URI problems similarly reported more life events, as well as more negative affect and neurotic emotionality.

In a study reported by Linville (1987), 106 undergraduates completed a life events measure (CSLES) and self-reported measure of illness and then reported illness data again 2 weeks later. With initial illness ratings controlled for statistically, those with more negative events were more likely to report having had the flu in the intervening period than those with fewer events. They were also more likely to report having other illnesses—illness in general as well as aches (could be flu related) and cramps. Negative events were not, however, associated with abdominal problems or with injuries.

Glaser et al. (1987) followed 40 first year medical students throughout the academic year. Students reported the number of days that their activities were restricted because of acute infectious illness during three high-stress (exam) and low-stress (1 month prior to exam) periods. More infectious (mostly URI) illnesses were reported during examination periods than during the preexam baseline periods.

Stone, Reed, and Neale (1987) studied 79 married couples who completed checklists of 80 life events (ADE) daily for 3 months. Daily life events rated as undesirable increased 3 to 4 days prior to onset of an URI episode (defined as 2 or more days of self-reported symptoms). Events rated as desirable decreased 4 to 5 days prior to onset. Finally, Imboden, Canter, and Cluff (1961) report data on *speed of recovery* from influenza. Psychological questionnaires (MMPI and CMI) were administered to 600 military employees. The study focused on the 26 members of this group who reported to the dispensary with flu during the following winter. Of the 26, those still reporting flu symptoms 3 to 6 weeks later had reported more symptoms of depression and emotional disturbance.

Overall, there is fairly consistent evidence for a positive relation between measures of both stressors (e.g., Glaser et al., 1987; Linville, 1987; Parens et al., 1966; Spilken & Jacobs, 1971; Stone Reed, & Neale, 1987) and distress (Imboden et al., 1961; Parens et al., 1966; Spilken & Jacobs, 1971) and URI-related illness behaviors. There is good reason, however, to question the extent to which these studies reflect stress-induced pathology as opposed to other (nonpathogenic) stress-induced processes that drive illness behaviors (see Figure 3). Of special concern is the fact that studies examining non-URI behaviors have found similar increases with stress for both URI and non-URI illness behaviors (Linville, 1987; McClelland et al., 1980; Spilken & Jacobs, 1971). This suggests that stress affects all illness behaviors rather than just behaviors specific to URI (see Pennebaker, 1982; Rabkin & Struening, 1976). However, there are also data indicating that stress associations with self-reported illness may be partly or wholly attributable to underlying pathology. Stone et al. (1987) found that stress may precede URI symptomatology by 3 to 4 days—close in time to the incubation period of many common cold viruses (24 to 72 h) and other studies indicate stress-induced changes in immunity as well as illness behavior (see work discussed later in the section on testing pathways; e.g., Glaser et al., 1987; McClelland et al., 1980).

Verified Upper Respiratory Infections

We turn now to studies in which URI was verified either by physician diagnosis or biological methods.

Retrospective studies. In a study by Jacobs, Spilken, and Norman (1969) undergraduates completed the LCI, BPI, and MARS. More physician diagnosed cases of URI were found among those with relatively numerous life changes. The effect occurred only for "personal failure and role crisis" events. URI incidence was also associated with greater defiance, danger-seeking behavior, and unpleasant affect. In another student sample, Alexander and Summerskill (1956) found no differences between stressful (e.g., exam and preexam) and nonstressful periods on campus and diagnosed incidence of URI. Nor were academic probation, university disciplinary action, or university activities related to URI incidence. However, persons seeking help at the mental health clinic had a higher incidence of URI than the sample as a whole. Finally, in a community study of children (mean age 4.3 years), Boyce et al. (1977) found that increased life events (as retrospectively reported by parents on a pediatric modification of the SRE) were associated with increased duration of illness and illness severity (as evaluated by health professionals) but not with number of illnesses. Moreover, contrary to prediction, children in families with unchanging daily routines were predisposed to greater stressor-elicited illness severity instead of protected from it.

Prospective studies. In an early study, Meyer and Haggerty (1962) followed 100 members of 16 families for a 12-month period. Family diaries were used to record stressful life events. Throat cultures (screened for streptococcal infections) were made every 3 weeks and at times of acute illness. Blood (for antibody levels) was drawn every 4 months. Daily life events that disrupted family and personal life were 4 times more likely to precede than to follow new streptococcal and nonstreptococcal infections and associated symptomatology. In addition, chronic family stress (as judged by observers) was related to greater numbers of new infections, prolonged production of the bacterium without symptoms, higher streptococcal illness rates, and elevated antibodies to a streptococcal-produced toxin (antistreptolysin O). Separate analyses indicated that a large group of control variables including sex, family history of respiratory infections, family size, and allergic history were unrelated to infectious outcomes.

Similar results were reported in a study of viral URIs in 235 members of 94 families (Graham et al., 1986). Diary data on respiratory symptoms were collected daily for 6 months. Major stressful life events (LEI) were assessed before and after the study period, and daily events (DHS) and psychological distress (GHQ) were assessed at study onset and twice during the study. Illness episodes were validated by viral cultures of nose and throat swabs, and analyses included controls for a wide range of

other factors such as sex, age, family size, and proneness to infection. High stress was defined as above median scores on *all three* stress measures: life events, daily events, and psychological distress. Those reporting higher levels of stress over the course of the study (retrospective analysis) experienced more verified episodes and more symptom days of respiratory illness. Those with higher levels of stress at the beginning of the study (prospective analysis) demonstrated similar but somewhat attenuated effects of stress on number of episodes and days with symptoms. In analyses designed to determine independent effects of the three stress measures, prestudy daily event frequency was positively associated with verified episodes, and prestudy life events were positively associated with the number of symptom days in verified episodes.

Two prospective studies have addressed psychological susceptibility to influenza. In the first (Cluff, Canter, & Imboden, 1966), 480 male employees of a military research installation completed the CMI and the hypochondriasis, morale loss, and ego strength scales of the MMPI 6 months before an epidemic of Asian influenza. On the basis of test scores, they were classified as either psychologically vulnerable or nonvulnerable. During the subsequent epidemic period, all persons presenting an influenzalike illness were followed over a 3-week period to evaluate acute disease. Infection was verified both through antibody increase and virus isolation. Illness reports in the psychologically vulnerable group were about three times higher than in the nonvulnerable group. However, there were no differences in infection rates or illness severity.

In the second flu study (Clover, Abell, Becker, Crawford, & Ramsey, 1989), 246 individuals in 58 families completed instruments assessing family relationships (Family Adaptability and Cohesion Evaluation Scales and Family APGAR) and individual stressful life events (SRRS) prior to the start of flu season. Antibodies to two strains of influenza B were measured before and after flu season. Incidence of illness was defined as a fever greater than 100°F, a criterion number of flu symptoms, *and* "influenza infection" (isolation of flu virus in throat culture or a four-fold increase in antibodies to Influenza B). They found that incidence of disease was greater in stressed ("rigid" and "chaotic") families than in nonstressed ("balanced") families. Incidence also increased as family cohesiveness increased, possibly because increased social contacts among family members result in increased exposure (Cohen, 1988). Illness incidence was not related to life events or family satisfaction.

In sum, evidence from studies verifying infectious episodes suggests that stress increases risk for upper respiratory disease. The retrospective work is fairly consistent in this regard, but the prospective studies are mixed. Two community based studies of families (Graham et al., 1986; Meyer & Haggerty, 1962) found support for reliable increases in verified disease with increased life events, although a third (Clover et al., 1989) did not. Two of these studies (Clover et al.; Meyer & Haggerty) similarly indicated evidence for greater incidence of disease among those with relatively high levels of family distress. Finally, Cluff et al. (1966) found that psychological distress was related to illness reporting, but not to verified illness.

Viral-challenge studies. Several studies have exposed healthy volunteers to specific viruses in attempts to determine whether psychological factors (measured prior to the viral challenge) influence susceptibility to URI. Advantages of this paradigm include eliminating the possible role of psychological effects on exposure (see Figure 1), controlling dosage of the infectious agent, and allowing biologic verification through tests for the specific virus used. For these studies to work, the *dose* of virus must be carefully chosen to result in a reasonable distribution of infected and uninfected persons. Although the optimal distribution depends on sample size and whether a dichotomized (infected or not) or trichotomized (not infected, infected without symptoms, infected with symptoms) outcome is used, a minimum of 20% in each group is usually required.

Four of the viral-challenge studies examined the role of stress in susceptibility to infection. In the first study (Totman, Kiff, Reed, & Craig, 1980), 52 healthy volunteers completed a stressful life events interview (modified procedure proposed by Brown, 1974) and the SRE. Subsequently, they were inoculated with two rhinoviruses (RV2 & RV31) and followed daily (in isolation) for 1 week. After controlling for prechallenge antibodies to the two rhinoviruses, total amount of virus shedding (extent of infection) was predicted by only one of five life event scores: Increased shedding (but not a combined measure of signs and URI symptoms) was associated with increases in total level of purposeful activity and social contact. None of the other stressor measures (including the standard SRE) were related to viral shedding or symptom scores. They also found that introverts (as assessed by the Eysenck Personality Questionnaire [EPQ]) had greater infection and symptomatology than extroverts.

In the second study, Broadbent, Broadbent, Phillpotts, and Wallace (1984) report data from 39 people receiving rhinoviruses (RV9 or RV9 + RV14) and 51 receiving influenza viruses (A Munich or A California). In the rhinovirus trials, people higher in introversion as assessed by the EPQ were more likely to demonstrate verified infection through viral isolation. Total clinical symptom score (combining both signs and symptoms) was predicted by obsessionality and by total psychological distress (MHQ). In the influenza trials, the total clinical symptom score was similarly predicted by greater obsessionality. However, infection (viral isolation) was not predicted by any of the psychological measures.

In the third study, Greene, Betts, Ochitill, Iker, and Douglas (1978) examined effects of self-reported life events (College SRE) and moods (POMS) in 33 subjects receiving nasal inoculations of an influenza virus (A Victoria) and the drug isoprinosine. Life events and mood states were assessed on Day 1; symptoms were rated on Day 1 and twice daily for the remainder of the week. On the second day, subjects received nasal inoculation of the virus. Neither life events nor moods were related to antibody production, viral isolation, or symptomatology. Similar results were found in a study with a larger sample. Locke and Heisel (1977) gave 124 volunteers a "swine" (A/NJ/76) flu vaccine and had them complete life events (SRE) and mood (POMS) scales. Again, no relations were found between the psychological measures and production of specific antibodies.

In another viral-challenge study, Totman, Reed, and Craig (1977) attempted to manipulate cognitive dissonance and assess its effects on susceptibility in 52 volunteers. Half the subjects were given a choice (dissonance) of receiving a "trial antiviral drug" and half were not asked (or given the drug). The design

called for all those in the choice condition to accept. Unfortunately, over half (56%) declined. Contrary to predictions, all persons offered the drug (whether or not they agreed to take it) had higher clinical symptom scores (combined signs and symptoms) than those not offered the drug. No differences were found for virus isolation. The interpretation of these results was that being presented with the decision of whether or not to take the drug was stressful, resulting in greater symptomatology.

In sum, viral-challenge studies provide mixed evidence for a relation between stress and susceptibility to rhinovirus infections and no evidence for a relation between stress and influenza. In light of support for a relation between stress and URI in prospective epidemiologic field data, the relative failure of viral-challenge studies to find consistent relations between stress and susceptibility to URI is difficult to interpret. It may be that field results are attributable to stress-induced social contacts resulting in increased exposure to infectious agents (see Figure 1), and hence, because viral-challenge studies control for exposure they do not find such results. However, methodological limitations of the challenge studies may also account for their failure in this regard. Individual studies suffer from insufficient sample sizes, concurrent administration of drugs, lack of information on overall rates of infection in response to the dose of virus administered, and controls for important predictors of susceptibility such as preexisting antibodies to the infectious agent, gender, and age (see Jackson et al., 1960).

It is interesting that two viral-challenge studies found relations between introversion and infectious outcomes. Introverts demonstrated a greater extent of both infection and symptomatology in the first study (Totman et al., 1980) and infection (but not symptomatology) in the second (Broadbent et al., 1984).

Summary: Overall, there is enough evidence supporting a relation between stress and onset of URI to suggest that further work is worthwhile, but not enough to draw definitive conclusions. There is strong evidence for an association between stress and illness behaviors and a reasonable amount of provocative field data suggesting similar effects for verified infectious disease. At this time, however, it is impossible to tell whether these latter results are attributable to stress-induced increases in exposure to URI pathogens or to stress-induced influences on immunity.

Herpesvirus Infections

A number of studies have addressed the role of psychological factors in human herpesvirus infection and recurrence of lesions. Included are studies of herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), Epstein-Barr virus (EBV), and Cytomegalovirus (CMV). HSV-1 is most frequently associated with cold sores, HSV-2 with genital lesions, EBV with infectious mononucleosis, and CMV with mononucleosis syndrome and deafness in neonates (Kiecolt-Glaser & Glaser, 1987a). However, herpesviruses can cause a range of illnesses. For example, HSV-1 can also produce generalized infections and encephalitis (Kiecolt-Glaser & Glaser, 1987a). Herpesviruses differ from most other known viruses in that after exposure, they are present all of the time, although often in latent states. Competency of cellular immune response is thought to be a critical factor in limiting primary herpes virus infection and in subsequent latent virus control (Glaser & Gotlieb-Stematsky, 1982).

Many of the studies in this literature address *reactivation* of herpes. Disease recurrence may be frequent, relatively rare, or never occur and is thought to be influenced by fever, exposure to the sun, hormones, and psychological factors such as stress (Laudenslager, 1987; VanderPlate & Aral, 1987). As discussed earlier (see the activation of latent pathogen box in Figure 2), stress influences on latent pathogens could be mediated by direct stimulation of pathogen reproduction (herpesvirus, in this case) or through suppression of immune defenses that hold the pathogen in check. Either of these processes could cause the immune system to produce antibodies to the virus. Research on susceptibility to herpes recurrence is particularly interesting because of the possibility that models of herpes activation may be relevant to understanding relations between stress and another latent virus, human immunodeficiency virus (HIV), the virus responsible for AIDS (Glaser & Kiecolt-Glaser, 1987).

Antibody increases with stress. A series of studies have examined reactivation of herpesviruses under stress (as measured by increased antibody response) in latently infected persons. These studies were *not* designed to investigate clinical herpes outcomes, and they do not include measures of herpes symptomatology. Moreover, because analyses examine differences between mean group changes in antibody levels, as opposed to comparing the number of individuals who show clinically significant changes, they are not entirely comparable to studies using antibody increase as an indicator of infection. They do, however, provide a consistent literature demonstrating sensitivity of latent herpesviruses to stressful situations.

Recall that activation of a latent pathogen can be detected by an increase in the production of antibodies in response to the activated virus. Studies of first year medical students indicate elevations of HSV-1, EBV, and CMV antibodies during and just prior to exam periods (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Glaser et al., 1987). When compared with nonstressed control groups, higher levels of herpesvirus antibodies have also been found among those exposed to other psychological stressors including elevated antibody levels to EBV among recently separated women (Kiecolt-Glaser, Fisher, et al., 1987), EBV and HSV-1 among separated and divorced men (Kiecolt-Glaser et al., 1988), EBV among caregivers of Alzheimers victims (Kiecolt-Glaser, Glaser et al., 1987), and HSV-1 among persons living near the Three Mile Island nuclear plant (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989) and depressed patients (Cappel, Gregoire, Thiry, & Sprecher, 1978; Halonen, Rimon, Arohonka, & Jantti, 1974; Rimon & Halonen, 1969; Rimon, Halonen, Anttinen, & Evola, 1971). Because herpesvirus activation is a necessary condition for disease recurrence, these data suggest that stress may play an important role in the progression of diseases caused by herpesviruses.

One could argue that increased antibody levels to latent herpesviruses are not a reflection of stress-induced herpes activation but instead merely reflect a nonspecific increase in serum antibody levels in response to stress. However, those studies that also assessed stress-related changes in common (i.e., to which almost everyone has been exposed) nonlatent viruses

such as poliovirus and rubella found no association between antibody levels of the nonlatent viruses and stressor exposure (Cappel et al., 1978; Glaser et al., 1985; Halonen et al., 1974; Kiecolt-Glaser et al., 1987; McKinnon et al., 1989). Hence, the data described earlier appear to indicate stress-induced antibody changes in response to latent but not nonlatent viruses.

HSV-1: oral herpes. Retrospective studies are mixed in their support for a relation between psychological distress and herpes recurrence. There was no relation found between distress (CMI) and verified ulcers in 343 students and 242 hospital patients (Ship, Brightman, & Laster, 1967). In contrast, positive relations were found between questions about depression and nervous troubles and self-reported recurrence in 1,133 medical and nursing students (Ship, Morris, Durocher, & Burket, 1960). Verified ulceration was also found to increase with distress in a study of only 10 patients (Schmidt, Zyzanski, Ellner, Kumar, & Arno, 1985). Greater retrospective reports of anxiety (POMS), daily hassles (DHS), and stressful life events (modified PERI) were reported for the weeks leading up to the recurrence of lesions than for weeks prior to dormant periods. There were no differences between dormant and active phases for coping, uplifts, Type A behavior pattern, and depression.

Early prospective support for stress-induced lesions was reported by Katcher, Brightman, Luborsky, and Ship (1973). These investigators administered the CMI, the Clyde Mood Scale, and a social assets scale to 38 young women entering nurse's training and then monitored them for 1 year. On entering the study, 37% had detectable HSV-1 antibody and 71% reported a history of cold sores. (It is probable that most if not all subjects in this study had latent HSV-1 infections that were not detected with a relatively insensitive technique [e.g., Glaser & Gotlieb-Stematsky, 1982]). The women were asked to report the onset of cold sores, and a subset of their reports were then verified by oral examination and HSV-1 viral isolation. Those reporting chronically unhappy moods had more verified episodes of herpes during the following year. Those with stronger social assests (social competence) had fewer episodes. Major stressful life events (LCI) were not related to reports of lesions.

An attempt at replication by this same research group was unsuccessful (Luborsky, Mintz, Brightman, & Katcher, 1976). In this case, the sample consisted of 43 young student nurses who were latently infected with (i.e., seropositive for) HSV-1. Subjects filled out the Clyde Mood Scale daily for 3 weeks and were checked daily for herpes sores on lips and herpesvirus in mouth secretions. A daily calendar was kept by each woman containing a notation of cold sores and other illnesses. Mood scores prior (and subsequent) to illness episodes were unrelated to the onset of herpes, upper respiratory infection, or aphthous ulcers. Moreover, neither mean mood scores (collapsing over all days of the study) nor variance in mood scores were related to illness incidence.

A final 3-year study of 149 student nurses by members of the same research group again found evidence for stress-induced virus reactivation (Friedmann, Katcher, & Brightman, 1977). At the onset of the study, antibodies to HSV-1 and history of primary and recurrent herpes infections were assessed. Participants also completed measures of enduring mood trait characteristics (Clyde Mood Scale). Incidence of herpes recurrence was reported on daily calendar forms (previous data had indicated that calendar reports of recurrence were consistent with documented lesions). Although the best predictors of recurrence were greater past incidence and HSV antibody levels, those reporting more unpleasant moods at study onset also had higher rates of recurrence. When rate of recurrence was predicted among only those with at least one episode, those with higher social assets scores had fewer episodes.

Overall, the oral herpes literature is inconsistent but suggestive. Disease episodes were preceded by measures of unpleasant moods in two prospective studies (Friedmann et al., 1977; Katcher et al., 1973). Both studies also found fewer episodes of disease among those with greater social competence.

HSV-2: genital herpes. In a retrospective study, Manne and Sandler (1984) found that persons reporting more symptoms of genital herpes also reported more stressful (negative) thoughts about having herpes, more depression (BDI), and lower self-esteem (Rosenberg Scale). Higher symptom reporting was also related to lower levels of social support, more characterological self-blame, more blaming the person who gave them herpes, and more wishful thinking as a coping strategy (Ways of Coping Scale).

Similarly, VanderPlate, Aral, and Magder (1988) studied 59 patients who reported that they had culture verified genital herpes. In this study life events (SRE) were found to be associated with increased self-reports of recurrence for those with low levels of herpes related social support and for those who had had the disease for less than 4 years. Recurrence for those with high levels of herpes related support and for those with the disease for more than 4 years was not associated with life events. A global measure of perceived stress designed by the authors was also associated with increased recurrence.

A study of 36 patients with chronic recurrent genital herpes was reported by Kemeny, Cohen, Zegans, and Conant (1989). They found that depressive symptoms (POMS subscale) were related to herpes recurrence only for persons without multiple recurrent infections, with greater symptoms associated with greater recurrence. Stress (linear combination of five stressor and distress scales) and the hostility and anger subscales of the POMS did not predict recurrence. Although longitudinal data were collected monthly for 6 months, data analysis was based on average of monthly outcome values across the study and hence is retrospective.

Two prospective studies provide evidence for stress-induced genital herpes recurrence, although both studies are methodologically flawed. Goldmeier and Johnson (1982) followed 58 patients for 28 weeks after diagnosis (virus isolation) of the first occurrence of genital herpes. Patients with higher psychological distress (GHQ) at the onset of the study had higher verified rates of recurrence. Unfortunately 13 of the 29 persons without recurrences were lost to attrition, leaving the possibility that distressed persons without recurrence may have dropped out of the study.

McLarnon and Kaloupek (1988) studied 16 genital herpes patient volunteers prior to beginning 5 weeks of psychologic therapy (T1), 1 week after therapy (T2), and again 12 weeks after therapy (T3). Anxiety (but not dysphoria) rates as assessed by the Hopkins Symptom Checklist were higher during the 4 days prior to a self-reported recurrence than during the 4 days after healing. Higher recurrence rates (daily reports during ther-

apy) were associated with higher loneliness (UCLA Loneliness Scale), less endorsement of denial and behavioral action as coping strategies (Ways of Coping Scale), and more positive attitudes about herpes at T1. There were, however, a large number of analyses in this study with no correction for Type I error.

In sum, genital herpes studies generally support a relation between stress and recurrence. However, the evidence is not entirely consistent, and methodological limitations of the two existing prospective studies lead to cautious interpretation of these results. There is some indication that the influence of stress may vary between samples whose subjects have many or few recurrences (Kemeny et al., 1989).

EBV: mononucleosis. As discussed earlier, most of the work with HSV-1 and HSV-2 has focused on recurrence in latently infected persons. In contrast, EBV studies have focused on the relation between psychological factors and having (retrospective) or developing (prospective) mononucleosis.

Two retrospective studies compared students diagnosed with mononucleosis with control groups diagnosed with other illnesses. Roark (1971) found few differences in emotional distress, personality (California Personality Inventory), and anxiety (Spielberger State Anxiety) between groups, whereas Wilder, Hubble, and Kennedy (1971) found that the mononucleosis group reported *fewer* life changes (college student SRE) than did both healthy and ill control groups. In a study of time to recover from mononucleosis, Greenfield, Roessler, and Crosley (1959) found that students with *longer* recovery periods reported higher levels of general psychological health (MMPI) when tested 6 months later than those with shorter recovery periods.

In the only prospective study of mononucleosis, a class of 1,400 West Point cadets was followed for 4 years (Kasl, Evans, & Niederman, 1979). Presence or absence of EBV antibody was used to identify those susceptible or immune to mononucleosis. New infections were identified by appearance of the antibody (seroconversion) in previously uninfected cadets. Cadets viewed as under stress because of a combination of high motivation and poor academic performance were more likely to seroconvert, to develop clinical mononucleosis if they seroconverted, and to spend more time in the hospital if they developed clinical infection.

Summary: Overall, evidence that reactivation of latent herpesviruses can be triggered by emotional distress is suggestive but not conclusive. Although the retrospective evidence is quite mixed, prospective support for stress-triggered reactivation comes from studies of oral (Friedmann et al., 1977; Katcher et al., 1973) and genital herpes (Goldmeier & Johnson, 1982; McLarnon & Kaloupek, 1988). Moreover, studies of changes in herpes antibody levels indicate HSV-1, EBV, and CMV antibody increases under stress. A single prospective study (Kasl et al., 1979) also indicates the possibility of stress-triggered primary infection. Evidence from four studies (Friedmann et al., 1977; Katcher et al., 1973; Manne & Sandler, 1984; McClarnon & Kaloupek, 1988) also suggests that social skills or social support is associated with fewer episodes of disease. Moreover, VanderPlate et al. (1988) found that persons with support for herpes did not demonstrate the increase in recurrence under stress found for those without support. Some of these studies suffer from methodological problems, and further prospective work with larger, more representative samples would be a welcome addition.

Bacterial Infections

Common respiratory bacterial infections were addressed in the section on URI (e.g., Meyer & Haggerty, 1962). Although there are hundreds of other infectious diseases caused by pathogenic bacteria, research on psychological influences on these diseases is relatively sparse and scattered. Retrospective studies have found relations between stressful life events and a variety of diseases caused by bacterial infections. Frequency of stressful life events has been associated with tuberculosis (Hawkins, Davies, & Holmes, 1957; Rahe, Meyer, Smith, Kjaer, & Holmes, 1964) and verified cases of trenchmouth (Cohen-Cole et al., 1981). Similarly, persons reporting a recent stressful life event had more frequent cavities (Sutton, 1962), and those reporting longer lasting events had more severe cavities (Sutton, 1965). Greater psychological distress has been reported by persons still experiencing "general symptomatology" 4 to 8 years after a diagnosis of acute brucellosis (undulent or Mediterranian fever) (Imboden, Canter, Cluff, & Trever, 1959) and by verified trenchmouth patients both during and after infection (Cohen-Cole et al., 1981).

A range of personality variables have been retrospectively correlated with severity of periodontal disease. Manhold (1953) found that those with more severe periodontal pathology were higher in neurotic tendency and introversion, and Formicola, Witte, and Curran (1970) found that dominance was positively correlated and succorance negatively correlated with disease severity. However, both studies used a large number of statistical tests and many other traits were unrelated to infection (Type I error).

In a single prospective (bacterial-challenge) study, 37 healthy male volunteers were exposed to typhoidal type tularemia (Canter, 1972). Tularemia is a plaguelike disease characterized by inflammation of lymph nodes, headaches, chills, fever, and vomiting. Subjects were defined as "psychologically vulnerable" if they scored above the median on at least three of four psychological distress scales (MMPI hypochondriasis, morale loss, and ego strength and the CMI) administered 2 days prior to exposure. Those scoring below the median on at least three scales were defined as "psychologically nonvulnerable". Prospective analysis indicated that severity of illness (defined as number of hours with fever over 100°F plus highest self-reported symptom scores) was higher for vulnerable than nonvulnerable and other subjects. They also report that 34 of the 37 subjects showed significant declines in positive mood (MACL) and increases in negative mood (MACL) at least 6 hours before onset of fever.

Summary. There are few studies of the role of stress (or other psychological factors) and bacterial infection, and existing data are spread across diseases. Although the retrospective studies vary in focus and quality, they are generally consistent with a relation between susceptibility to bacterial infection and stress. It is also promising that the two prospective studies on bacterial infections—the Meyer and Haggerty (1962) study discussed in the URI section and the Canter (1972) bacterial-challenge

study on tularemia—both find evidence for relations between stress and disease incidence.

Testing Pathways

Earlier, we proposed that stress (and other psychological factors) could be linked to infectious disease through behavioral, hormonal, and immune pathways, as well as through direct CNS-immune innervation. Only a handful of studies assess a proposed pathway *in addition to* stress and infectious disease measures. (As discussed earlier, some of the individual paths, for example, the relation between stress and immunity, have been studied separately but have not been shown to mediate stress influences on disease.) Only one study (Kemeny et al., 1989) provides direct tests (e.g., path analysis or structural equation models) of whether covarying effects actually mediated reported relations. Hence, at best, these few studies can be considered consistent with the possibility that examined pathways are involved in linking stress to disease.

Endocrine Pathways

Two retrospective studies examined endocrine pathways. Both assessed hormones known to be released under stressful conditions. These hormones have also been implicated in immune modulation. Recall that McClelland, Floor, Davidson, and Saron (1980) found that persons high in stress, need for power, *and* action inhibition reported more illnesses and more severe URIs. This group also showed marginally less epinephrine (but not norepinephrine). Cohen-Cole et al. (1981), who found relations between trenchmouth and more life events and psychological distress, also found that levels of overnight urine cortisol were higher for those with more life events and for those diagnosed with trenchmouth. Serum cortisol, prolactin, growth hormone, and urine catecholamines were not correlated with either psychological distress or trenchmouth.

Health Behavior Pathways

Three studies measured health practices. Recall that Graham et al. (1986) found that stress predicted URI. The high-stress group also contained more smokers than the low-stress group; however, there were no direct tests of the relation between smoking and URI in this study. Kemeny et al. (1989) found a relation between depression and genital herpes recurrence, but failed to find any relations between recurrence and number of hours sleep and average hours of exercise. Although alcohol consumption was positively correlated with recurrence rate, a regression analysis indicated that it did not mediate the effect of depression on recurrence. Finally, Glaser et al. (1987) found less sleep and less exercise preceded exam periods. However, the differences were small, and there were no direct tests of the relations between these behavioral changes and reports of illness.

Immune Pathways

Several investigators have examined possible immune pathways. McClelland et al. (1980) found that persons high in stress, need for power, and action inhibition reported more illnesses and also had lower concentrations of total (to all antigens) salivary immunoglobulin A (IgA). IgA is a secretory antibody that, when specific to the infectious agent one is exposed to (as opposed to total IgA as assessed in this study), would theoretically help protect against infection (see Jemmott & McClelland, 1989; Stone, Cox, Valdimarsdottir, & Neale, 1987). In McClelland et al. (1980) those excreting more epinephrine also had lower concentrations of IgA. Correlations between IgA and illness frequency and illness severity were not, however, significant. In another study, McClelland et al. (1982) found that people with both high need power and high stress reported more severe illnesses, had lower concentrations of total secretory IgA, and that those with more severe URIs also had lower IgA concentrations.

Recall that Glaser et al. (1987) found more reports of infectious illnesses during medical student exams than during baseline periods. Exam periods were also characterized by poorer cellular immune control of a latent herpesvirus and a decline in the ability of white blood cells to kill EBV infected cells indicating a general suppression of cellular immune function. Exam stress was also associated with an increase in intercellular levels of cyclic adenosine monophosphate, a chemical released within cells in response to hormones and associated with suppression of immune function in lymphocytes (white blood cells central to immune response). Associations between immune measures and illness were not reported.

Kemeny et al. (1989) found a relation between depressive symptoms and genital herpes. Depression was also related to decreases in the CD8 population of T-lymphocytes and decreases in the CD8 population tended to precede herpes recurrence. The CD8 population consists of T-cytotoxic cells that can kill virally infected cells and T-suppressor cells involved in down-regulation (suppression) of immune response. However, further analyses indicated that changes in the CD8 population did not mediate the relation between depression and herpes recurrence. Finally, Cohen-Cole et al. (1981) found that those with trenchmouth demonstrated deficits in function of several types of white blood cells including lymphocytes, polymorphonuclear cells, and phagocytes. Relations between stress and immune measures were not reported.

Summary

It would be premature to suggest that any of this evidence is more than suggestive of the role of behavioral, endocrine, and immune mechanisms in linking stress to infectio. disease. However, we applaud these investigators' interest in specifying and measuring pathways linking stress to infectious disease and hope that future research will examine alternative pathways in more detail and with greater sophistication in analysis.

Discussion

The literature reviewed in this article suggests that stress may play a role in the onset of infectious diseases and reactivation of latent viruses. First, there is consistent evidence that persons under stress report greater levels of URI symptoms and that stress results in greater health care utilization for URI. As discussed earlier, the illness behaviors used as criteria in these

studies may tap underlying pathology but in some cases may be driven by purely psychological mechanisms (see Figure 3). The latter interpretation is reinforced by studies in which effects of stress on symptoms but not verified disease were observed (Broadbent et al., 1984; Cluff et al., 1966; Imboden et al., 1959) and by evidence that stress is associated with increased illness behavior in general, not only behaviors directly associated with infectious pathology (e.g., Linville, 1987; McClelland et al., 1980; Spilken & Jacobs, 1971; also see review by Andrew & Tennant, 1978). Even if stress links to illness behavior do not have pathogenic origins they are theoretically and practically important. From a theoretical perspective there are implications for understanding how people perceive and understand their physical states as well as indicating a specific role of stress in life satisfaction. From a practical perspective, there are implications for health-care policy such as the advantages of employing triage procedures to separate those with underlying pathogenesis from those without so that medical personnel can be used most efficiently.

Second, there is evidence suggesting that stress increases risk for verified upper respiratory infections. The most impressive data are from two prospective community-based studies (Meyer & Haggerty, 1962; Graham et al., 1986). On the other hand, prospective URI viral challenge studies do not generally support a relation between stress and URI. The cause of this relative failure may be that by controlling for *exposure* to the pathogen (an important operative pathway in the stress–infection link to URI) was eliminated. However, the methodological limitations of these studies (outlined earlier) may also account for their failure in this regard.

Third, there are only scattered studies of the role of stress in bacterial infections. Retrospective studies of tuberculosis, brucellosis, periodontal disease, and acute caries all suggest associations between stress and disease. Moreover, the only bacterial (tularemia) challenge study (Canter, 1972) and the only prospective study focusing on bacterial (streptoccocal) infections (Meyer & Haggerty, 1962) both indicate increased risk for disease among high-stress persons.

Finally, there is growing evidence that stress may trigger *reactivation* of herpesviruses, hence recurrence of disease among those with previous exposure to herpes. Support for stress-triggered reactivation comes from a series of studies indicating increased antibodies to three herpesviruses under stress (e.g., Glaser et al., 1985; Glaser et al., 1987) and from prospective studies of oral (Friedmann et al., 1977; Katcher et al., 1973) and genital herpes (Goldmeier & Johnson, 1982; McLarnon & Kaloupek, 1988). A single prospective study (Kasl et al., 1979) also indicates the possibility of stress-triggered primary infection. The methodological sophistication of these studies is inconsistent, and further prospective work with larger, more representative samples is needed.

Are These Studies Measuring Stress?

Studies in this literature are primarily based on self-reported events and psychologic distress. Consistent with our conceptualization of events and distress as reflecting different stages of a single process, these measures seem to be roughly equal in their reliability as predictors of infectious outcomes. Prospective studies of daily or weekly events (Meyer & Haggerty, 1962), family stress (Clover et al., 1989; Meyer & Haggerty, 1962), and psychological distress (Canter, 1972; Friedmann et al., 1977; Goldmeier & Johnson, 1982; Graham et al., 1986; Katcher et al., 1973; McLarnon & Kaloupek, 1988) have all predicted verified disease outcomes. This may be because stressful events (as assessed in these studies) generally result in distress, or because self-reports of events are inherently confounded with existing distress (Costa & McCrae, 1980).

These results must, however, be viewed in the context of the limitations of self-reported cumulative measures of stressors and distress. First, it is difficult to know whether these measures assess state or trait distress. It is possible that in many of the studies, life events and psychological distress measures reflect *stable personality styles* (negative affective or neurotic) more than impact of environmental stressors (e.g., Costa & McCrae, 1980, 1985; Watson & Pennebaker, 1989). Studies using between-subject designs—retrospective studies and prospective studies assessing stress only at study onset—are most susceptible to such an interpretation. Within-subject designs—comparing the same person under stress and nonstress conditions—are not susceptible. Because our models of the relation between stress and infectious disease are driven by negative affective state rather than the stressor itself, they also apply to a personality interpretation. However, there are enough within-subject studies in the literature to suggest that neurotic personalities are not the only things operating here (e.g., in nonverified disease studies by Glaser et al., 1987; Stone et al., 1987; in verified studies by McLarnon & Kaloupek, 1988; Meyer & Haggerty, 1962; and in all of the herpes antibody studies, e.g., Kiecolt-Glaser, Fisher, et al., 1987; Kiecolt-Glaser, Glaser, et al., 1987).

Second, the existing literature does not provide the strongest possible test of the hypothesis that stress influences pathogenesis of infectious disease. Cumulative stress scales used widely in this literature, for the most part, tap levels of stress within the normal range of variations that people experience in day-to-day life. Impact of severe events would provide the fairest test of a stress–disease relation. Restriction of stress variance is a particular problem in student samples that represent a cohort experiencing few traumatic events (Schulz & Rau, 1985). Given this, it is impressive that cumulative event and distress scales are related to disease outcomes. Further work using more sophisticated techniques for measuring life events in the context of their meaning for the individual (see techniques developed by Brown & Harris, 1989) and examining effects of single stressful events (e.g., Alexander & Summerskill, 1956; Glaser et al., 1987), especially more serious and even traumatic events (e.g., divorce, bereavement, and job loss) would significantly strengthen this literature (see Kasl, 1984).

Other Psychological Variables and Infectious Disease

Although a number of factors were associated with disease in one study or another, two variables—introversion–extroversion and social support—were related to infection across a number of studies. Introverts were more susceptible to infection or more severe illness (Broadbent et al., 1984; Manhold, 1953; Totman et al., 1980). Persons with social skills or social support

had fewer episodes of disease (Friedmann et al., 1977; Katcher et al., 1973; Manne & Sandler, 1984; McClarnon & Kaloupek, 1988), and those with social support did not demonstrate the positive relation between life events and a chronic URI episode (Sarason et al., 1985) and life events and herpes recurrence (VanderPlate et al., 1988) found among those without support. A single study (Clover et al., 1989) found *more* disease episodes in cohesive families; a finding we interpreted as attributable to increased social contacts resulting in increased exposure to infectious agents. It is possible that introversion–extroversion and social support reflect a single underlying construct—an outgoing (extroverted) personality that results in less susceptibility to infection, either because such persons are good at drawing resources from their social networks (Cohen, 1988) or because of some other biological or social correlate of introversion–extroversion.

Stress–Immune-Disease Specificity

Stress influence on immunity is considered by many to be the primary pathway through which stress influences infectious disease susceptibility. Specific stress-induced changes in immune function that lend persons susceptible to infection have not been delineated. However, it is commonly believed that different stressors have the same influence on immune function (Mason, 1975, assumes nonspecificity is mediated by psychological distress; Selye, 1956, does not) and that stress induced changes in the immune system result in susceptibility, to most if not all infectious agents (e.g., Cassell, 1975). One test of these nonspecificity assumptions is equivalent influences of stress across diseases. The current literature is very roughly supportive of equivalency—distress and stressful life events influencing susceptibility to different pathogens—but there are too few studies and too few infectious diseases examined to provide an answer to the specificity question at this time. Moreover, there are data in the animal literature indicating that nonspecificity assumptions may be incorrect. Work with rodents suggest that immune responses may differ across stressors and that the same stressors influence susceptibility to some but not other pathogens (Friedman et al., 1965; Friedman, Glasgow, & Ader, 1969; Rasmussen, Marsh, & Brill, 1957). A single study comparing different specified pathogens in humans (Broadbent et al., 1984) reported some similarities and some differences in the effects of psychological measures on rhinoviruses and influenza viruses. Future work comparing the influence of various pathogens in humans, in the same stress paradigm, and examining the effects of different stressful events on the same disease would provide welcome evidence in relation to this important question.

Where Do We Go From Here?

The work reviewed in this article suggests that stress may influence both infectious illness behaviors and infectious pathology. However, it tells us little about how stress influences pathology, the nature of stressors that put persons at risk for disease, timing of the stressor relative to exposure and disease onset, and psychological and biological characteristics that may moderate these effects.

Behavioral and Biological Pathways

Existing work reveals little about the pathways outlined in Figures 1 and 2. Further epidemiologic-style studies assessing pathways *and* using appropriate statistical tests for mediation could make a major contribution to this area. Moreover, experimental studies in which individual pathways are eliminated, for example, exposing all volunteers to an infectious agent or blocking hormonal or immune pathways through the use of drugs (e.g., Bandura, Cioffi, Taylor, & Brouillard, 1988), could also help identify operative mechanisms.

Temporal Courses of Stressor, Mediators, and Disease Pathology

If there is a major barrier preventing a general understanding of relations between stress and infectious disease, it has to do with time. We know little about time courses of many processes central to stress–disease models. Relative to exposure to an infectious agent, when (e.g., before, during, or after) is stress most likely to influence susceptibility? How long an exposure to stress is required to alter biologic or behavioral pathways to disease? How long must these pathways be altered to influence subsequent pathways, for example, hormone levels altering immunity? How long must the most proximal pathways be altered to influence disease susceptibility? How long after a stressor is terminated do these changes last?

Evidence from experimental studies in which mice are randomly assigned to stress or control conditions and exposed to an infectious agent indicate that timing issues are complex (Friedman et al., 1965; Plaut & Friedman, 1981; Rogers, Dubey, & Reich, 1979). For example, stress *prior* to exposure may either increase resistance (e.g., Friedman et al., 1969; Jensen & Rasmussen, 1963a; 1963b) or susceptibility to infection (e.g., Friedman et al., 1969; Plaut, Ader, Friedman, & Ritterson, 1969). However, stress experienced *after* exposure to a pathogen generally increases susceptibility (e.g., Chang & Rasmussen, 1965; Davis & Read, 1958; Friedman et al., 1969; but see Friedman, Ader, & Grota, 1973; Rasmussen, Hildemann, & Sellers, 1963 for exceptions). As we discuss later, the issue of timing makes manipulating stress in studies of humans difficult at this time. It also suggests that correlational studies should be carefully planned to assess different temporal relations between stress and infectious outcomes (e.g., Stone, Reed, & Neale, 1987) or to focus on chronic or cumulative stressors resulting in relatively long-lasting psychological distress and maximizing length of exposure (Cohen & Matthews, 1987).

Chronicity of Stressors and Disease Risk

The effects of stressors presumably depend on their chronicity: acute, chronic, or repetitive. Because scales used in this literature often combine these different categories and focus on cumulative effects, little information on how single stressors influence disease is available. Effects of an acute stressor presumably would depend on its concordance with the pathogenic process (Cohen & Matthews, 1987; Cohen & Syme, 1985). For example, if stressors operate by increasing exposure to pathogens, an acute stressor occurring after exposure would not influ-

ence pathogenesis. It may be that questions of timing are not of major importance in the existing human literature because most studies assess chronic distress. Because persons are under stress for a prolonged period, the minimum exposure necessary to affect a pathway is exceeded. Studies more carefully characterizing stressor chronicity and timing could help clarify conditions under which stress influences disease susceptibility.

Prospective Infectious-Challenge Studies

Although the challenge studies reviewed in this article have not been particularly successful, we still feel this paradigm provides the best current strategy for pursuing the role of stress in infectious disease susceptibility. As noted earlier, it allows for control of previous exposure (through antibody measurement), control of current exposure (through experimental challenge), and careful assessment of both infection and symptomatology. Future work can capitalize on past mistakes by examining each pathogen separately, controlling for extraneous factors that may influence disease susceptibility (e.g., age, gender, season, history of infection), using large numbers of subjects, and carefully selecting psychosocial instrumentation to reflect plausible effects.

Manipulating Stress

A powerful test of the hypothesis that stress influences infectious pathology is to randomly assign persons to stress or nonstress conditions and assess subsequent susceptibility to infection. Such a technique, in the context of an infectious-challenge trial where exposure to the agent (and amount of infectious agent) is controlled, would provide a strong test of the role of stress in susceptibility. This design is not, however, without problems. Some guessing and piloting would be required to determine type of stressor to use, duration and intensity of exposure, and timing of exposure in relation to infectious challenge. Moreover, both ethical and practical limitations on type and intensity of experimental stressors may limit the probability of finding an effect.

One approach to addressing the problems involved in conducting experimental research in humans is to move to a nonhuman primate model. Unlike rodents, these animals can be exposed to chronic social stressors that are analogous to those encountered by humans (e.g., Coe, Rosenberg, & Levine, 1988; Laudenslager, 1988; Manuck, Muldoon, Kaplan, Adams, & Polefrone, 1989). Moreover, their behavioral responses to social stressors (e.g., affiliation and aggression) also are similar to human response patterns. Studies in which monkeys are randomly assigned to social stressor or nonstressor groups, are assessed for hormonal and immunologic change, and then exposed to an infectious pathogen (e.g., a cold virus) could provide important evidence to substantiate the human correlational research.

Moderators of Stressor–Disease Relations

Effects of stressors on disease may be moderated by social (Cohen & Wills, 1985), personal (Cohen & Edwards, 1989), and biological (Schleifer et al., 1986) factors. Social and personal characteristics are thought to influence whether stressful events result in psychological distress, although they may influence manifestations of distress such as behavioral and neuroendocrine response (Cohen & Wills, 1985). Biologic characteristics may influence susceptibility of immune and other disease-relevant biologic systems to CNS, hormonal, and behavioral changes triggered by stress. It is of particular interest that stress may have its greatest effect among those whose immune systems are already compromised (e.g., the elderly), individuals whose health is already impaired, and patients with immunosuppressive diseases (e.g., AIDS; Kiecolt-Glaser & Glaser, 1987b).

Summary

The relation between stress and infectious disease is extraordinarily complex. Assumptions about parametrics of the relation are premature and potentially damaging to our long-term understanding of the role of stress in human disease susceptibility. A slow and cautious approach in which each relation between a stressor, a specific pathway, immunity, and disease is systematically examined would be most likely to yield valid answers. This strategy could be complemented by experimental work with nonhuman primates.

Conclusion

The literature reviewed in this article is provocative. It suggests that stress is associated with increases in illness behaviors and may be similarly associated with increased onset and reactivation of verified infectious disease. Weaknesses in the existing work include designs limiting causal inference, unrepresentative samples, and lack of adequate examination of potential pathways linking stress to disease. This work indicates that studying this issue is a complex endeavor and that interdisciplinary collaboration is required to design adequate tests of the hypothesis that persons under stress are at higher risk for infection. Further pursuit of this question is justified—especially work using designs that allow us to address numerous remaining ambiguities and unanswered questions.

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Received September 18, 1989
Revision received May 9, 1990
Accepted June 15, 1990 ■