Stress and Disease Processes

Perspectives in Behavioral Medicine

Edited by
Neil Schneiderman,
Philip Mccabe and
Andrew Baum

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DISEASE PROCESSES

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PREFACE

As we have learned more about the relationships between stress and illness, we have been able to clearly delineate pathways by which stress may interfere with health maintenance and contribute directly to disease etiology and progression. Sympathetic nervous system arousal that drives many of the biological sequelae of stress appears to affect atherosclerosis, hypertension-related blood pressure changes, and a host of other pathogenic processes important in behaviorally-mediated disease. Although much of the research in behavioral medicine has focused on stress-related physiological changes and heart disease, there are rapidly growing research efforts addressing immune and endocrine changes and their effects on infectious disease, AIDS, diabetes, and other diseases.

A second pathway by which stress may alter health is less direct. We know that stress affects behavior in ways that can affect health. For example, it is widely believed that stress increases already established drug use, including cigarette use, caffeine consumption, and use of alcohol. To varying extents, such behavior appears to contribute to disease. Similarly, stress may interfere with important health-maintenance activities: Exercise, diet, and other valuable behaviors may decrease or disappear during or after substantial stress. In addition, specific regimens designed to prevent or control already established disease may not be followed during stress-related episodes of negative affect or disruption of daily routine. Thus, maintenance of preventive behaviors or use of drugs to control diseases such as diabetes or hypertension may be more difficult during stress.

A third pathway is closely related to the second. Illness behavior, loosely defined as actions that characterize ill individuals or that affect treatment, also appears to be affected by stress. Use of insulin to control diabetes or adherence to antihypertensive medical regimens could also be considered here, but other aspects of illness behavior are affected as well. Seeking medical attention when symptoms warrant it, detection and interpretation of symptoms, adherence to various regimens, and several other aspects of effective health behaviors appear to be vulnerable to stress-derived interference.

The chapters in this book are concerned with these different pathways, focusing on direct effects of stress on the immune and endocrine systems, on behavioral factors in diseases such as cancer and diabetes, and with the general role of stress in illness processes. We believe that they push beyond the well-staked boundaries of traditional models of disease and that like the Academy of Behavioral Medicine Research meeting that the book is based on, the authors have a good deal to say that is new and important. Continued study of these and other stress-related processes will provide critical data for preventing and treating modern epidemics.

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1 Acute and Chronic Stress and the Immune System

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The relationship between stress and health has long been one block in the foundation of behavioral medicine research and intervention. The contribution of stress to a wide variety of physical illnesses and to mental health are widely believed to be important, and research has addressed stress as a factor in heart disease, hypertension, stroke, cancer, and many other illnesses. Hormonal changes, hemodynamic responses, and other bodily reactions during stress have been considered to be risk factors for illness. Of some interest is the relationship between stress and immunity and whether the changes that have been observed are meaningful. Yet, we still know relatively little about how stress affects immune function, why such effects occur, and whether these changes have any real clinical significance.

One problem has been the relative dearth of research on human subjects, at least until recently. Most work through the 1970s was concerned with animal populations and, although extremely important in revealing links between behavioral factors and immune response (Ader & Cohen, 1981), it provided an imperfect model of stress and immune function in humans. Related to this is the fact that most work with humans considered subjects who had been victimized or exposed to stressful conditions, be they bereaved, caregivers for seriously ill people, medical students facing examinations, or divorced and/or separated spouses. Relatively little research has addressed acute stress in humans and has examined the effects of experimentally applied stress on normal volunteers. The generalizability of the results of studies of intermediate or long-term stress on immunity to short-term events and the meaning of good or poor correspondence across stress durations remains undetermined. This chapter selectively reviews research on animal and human immunological responses during acute and chronic stress to establish how well they correspond and whether one can consider acute and chronic stress as comparable in this instance.

Distinguishing between chronic and acute stress and gauging the severity and duration of stress effects is a complex task. Depending on an individual's experience when he or she is exposed to a stressor, the duration of the psychological and physiological responses may vary. This variation in response duration may depend on the ability of the organism to adjust to an event as much as on the duration or severity of the stressor (Baum, O'Keeffe, & Davidson, 1990). Acute stress may generate brief responses as the stressor passes or as adjustment to the event occurs. However, some acute events, such as traumatic events, may cause long-term responses that outlast the event itself. Similarly, chronic stressors may foster responses that last for a long time due to chronic exposure to an intractable situation or to failure to adjust, but may also lead to adaptation and cessation of stress responding while the stressor persists (Baum et al., 1990). Thus, acute stressors to which adjustment is difficult may generate long-term responses just as chronic stressors may cause chronic responses, and either may generate only brief responses. In addition, there are psychosocial mediators that affect adjustment to the stressful situation, by buffering the distress associated with the stressor (e.g., having perceived control over the stressor) or by augmenting distress associated with the stressor (e.g., by being lonely or depressed). Because it is likely that the duration of stress responding may affect the ways in which stress affects health, determination of these aspects of stress are important.

The complexity introduced by these concepts eliminates the elegance of simplicity, but increases their descriptive power. Although it may be more difficult to convince skeptics that basic stress–immune system relationships exist and are meaningful if we must qualify answers to these questions, the role of psychosocial mediation of this link provides clues as to preventive or ameliorative responses to stress-induced immunosuppression. Social support, efficacious coping, distress reduction, and other putative mediators of stress are potentially important in this effort.

We have divided the chapter into four sections, separately discussing animal and human studies of acute and chronic stress. It is difficult to classify some studies: Duration of stressor exposure varies greatly and distinctions between acute and chronic may become arbitrary at some level. Further, the duration of stress response does not necessarily match that of stressor exposure. These issues have led to extended analyses of chronic stress that are beyond the scope of this chapter (see Baum, 1990). Regardless, studies fall more or less into these categories and provide useful insights into the nature of stress and its health consequences.

ACUTE STRESSORS AND IMMUNITY

In psychophysiological studies of stress, acute laboratory exposure to stressful conditions is more common than are longer term or naturalistic studies of stress. This is particularly true of human studies where ethical and logistical concerns make the latter more difficult. In studies of stress and immune function, the reverse seems true; relatively few studies of acute stress and immune function in humans have been reported. To some extent this may be due to the time course of immune system changes: If these changes do not occur for several hours after exposure to a stressor, one must keep subjects in the laboratory and prevent potentially contaminating events for a long period of time. If they occur more rapidly, however, these studies can and should be pursued.

Animal Studies

In many animal studies simple physical events such as electric shock or immobilization have been used to generate stress and affect immune function (Gisler, 1974; Harmsen & Turney, 1985; Keller, Weiss, Schleifer, Miller, & Stein, 1983; Laudenslager, et al., 1988; Shavit, Lewis, Terman, Gale, & Liebeskind, 1984). For example, Harmsen and Turney (1985) exposed rats to 3 hours of intermittent shocks of one shock per minute. Neutrophil function was measured and results indicated that stressed rats demonstrated poor accumulation at a zymosan (yeast cell fragment) injection site compared to control rats. Acute physical stressors have also been found to decrease natural killer cell activity (Shavit et al., 1984) and lymphocyte proliferation to mitogen challenge (Keller et al., 1983). It is likely however, that physical stressors are emotionally arousing and that some of the consequences of these stressors are psychologically mediated (Mason, 1975). Being restrained or shocked is an aversive event that may involve psychological reactions as well as sensations associated with physiological changes.

The perception of a stressor as threatening may be necessary for stress responses to occur and therefore adjustment to a stressful event may only result if the stressor is no longer perceived as threatening (Mason, 1975). Kant and her colleagues (1984) have also suggested that response habituation results from behavioral experiences with a particular stressor, and not to biochemical adaptation or habituation of endocrine and neurotransmitter systems after repeated use. When rats were exposed to 15 minutes of restraint, footshock, or forced running for 10 consecutive days it was found that prolactin and pituitary cyclic AMP responses to each stressor gradually diminished and all but disappeared by the Day 10. However, those exposed to a novel stressor on Day 11 showed fully restored responses, whereas those exposed to the same stressor on Day 11 showed little response (Kant et al., 1984). Thus, exposure to a new stressor elicited an augmented hormonal and neurochemical response, whereas there was a diminished biochemical response to the same stressor experienced previously. This suggests that behavioral experiences with a particular stressor may lead to habituation but that this is not due to biochemical adaptation to stressors.

Acute psychosocial stressors have also been examined in animal populations and their relationship to changes in immunity measured. Fleshner, Laudenslager, Simons, and Maier (1988) studied immunological changes associated with brief bouts of territorial invasion. Rats living singly in plexiglass enclosures were divided into two groups: (a) animals who were directly exposed to aggressive rats living in a colony in pairs, and (b) animals who were separated from the colony groups by a barrier. Immediately before the first colony exposure, the intruders in both groups were immunized with keyhole limpet hemocyanin (KLH). The intruders were then exposed to five different colonies, each for 10 minutes. Intruders who directly interacted with aggressive colonies had lower levels of KLH serum IgG antibodies 1 and 2 weeks after immunization than the controls, suggesting that the animals exposed to a stressful situation (i.e., repeated confrontation with aggressive rats) were less able to launch an immune response against the KLH antigen. Apparently this was due to repeated exposure to dominant others, as those rats who reacted to the aggressive encounters by assuming more submissive postures had the lowest levels of antibody to KLH. Submissive posturing was associated with the frequency of being bitten but this variable was not correlated with KLH IgG levels. And, although the duration of the stressor exposure was acute (five, 10-minute exposures) differences in antibodies were still found 2 weeks later.

One way in which acute stressors may cause responses that outlast their physical presence is through conditioning, wherein neutral stimuli present during stressor exposure come to elicit responses independent of the stressor. Similar to the conditioned immunosuppression phenomenon (Ader & Cohen, 1981), the idea here is that the neutral stimuli could come to evoke immune responses or change responses when the stressor is no longer present. One study paired electric shock with an unrelated stimulus to determine if it would come to elicit similar immune changes when presented alone (Lysle, Cunnick, Fowler, & Rabin, 1988). Experimental animals were exposed to pairings of shock and either a clicking sound or flashing light. Ten presentations of the shock (5 seconds each) and conditioned stimulus (15 seconds each) were administered on consecutive days. Control animals were exposed to similar pairings of neutral and aversive stimuli but were not exposed to the conditioned stimulus (CS) during the test phase. After a

6-day recovery period the experimental group was given a test session of 10 presentations of the stimulus without shock.

Lymphocyte proliferation to mitogen challenge with concanavalin-A (Con A) and phytohemagglutinin (PHA) was suppressed following exposure to the CS. This suppression of proliferation was reduced during extinction when the conditioned stimulus was repeatedly presented in the absence of footshock. Additionally, pretreatment with repeated exposure to the conditioned stimulus before pairing with shock was found to lessen immune effects when the conditioned stimulus was later presented alone.

Psychosocial Mediators. Psychosocial variables influence the impact of stressors and immunological sequelae of stress. Studies have examined psychological mediators that may buffer the effects of stressors; control or lack of control over stressors appears to be one such factor. Laudenslager (1983) observed lymphocyte proliferation to Con A and PHA following acute exposure to escapable or inescapable shock. Twelve rats were placed in a "wheel-turn" box and shock was given through tail electrodes on an average of one shock per minute for 80 minutes. The shock could be terminated by moving the wheel. Twelve more rats were each yoked with the escapable shock subjects and therefore received comparable amounts of inescapable shock. A home cage control group was also studied. Twenty-four hours later the rats in the two experimental groups were given five 5-second footshocks and blood was collected from all animals. Inescapable shock led to a suppression of lymphocyte proliferation to PHA in comparison to escapable shock and control procedures. The Con A-stimulated cultures revealed somewhat different results; inescapable shock depressed lymphocyte proliferation but escapable shock appeared to increase lymphocyte proliferation.

A similar study examined stressor (shock) controllability and its relationship to proliferation of lymphocytes to mitogen challenge (Mormede, Dantzer, Michaud, Kelly, & LeMoal, 1988). Splenic lymphocytes were examined instead of peripheral blood lymphocytes and in vivo antibody response to sheep red blood cells (SRBC) injected into the rats was measured as a function of stressor controllability. Animals in the controllable stressor group were able to postpone electric shocks by jumping over a barrier. Yoked animals were run at the same time and received the same amount of shock at the same intervals as the controllable stressor animals but were not able to regulate when the shocks would be administered. Control rats were placed in comparable settings but received no shock.

Lymphocyte response to PHA was significantly reduced in animals that had no control over the stressor relative to the controllable stressor or control groups, which were comparable. There were also significant differences in antibody titer levels to SRBC but these findings were seemingly inconsistent; animals in the controllable stressor group had lower antibody titers than did controls or animals in the uncontrollable stressor group. In observing decreases in antibody titer formation to SRBC in the controllable stressor group without changes in proliferation and depression of lymphocyte proliferation to PHA it is important to note that consequences of controllability may vary depending on the type of immune response measured.

Uncontrollable shock may also affect immune-mediated health outcomes such as tumor development. Visintainer, Volpicelli, and Seligman (1982) examined tumor rejection in male rats exposed to inescapable or escapable shock, or not exposed to shock. Tumor cells were injected subcutaneously into the left lower anterior flank of each animal and 24 hours later each was exposed to shock or no-shock conditions. In the two shock conditions 60 random shock trials were delivered to the grid floor and sides of two identical chambers. Pressing a bar in the controllable shock chamber terminated the shock in both boxes, but depressing the bar in the inescapable shock chamber had no effect. Only 37% of the rats exposed to escapable shock, compared to 46% of the rats given no shock and 73% of the inescapable shock animals developed tumors. Thus, rats exposed to inescapable shock were considerably less likely to reject the tumor as rats in the escapable shock condition. Visintainer et al. (1982) suggested that differences in immunocompetence was probably an important factor in fighting against the tumors.

Stressor predictability is related to control: Predictability may not increase instrumental control but appears to facilitate adaptation by permitting preparation and anticipating responses. It also appears to be related to immune system changes (Mormede et al., 1988). A predictable signaled shock condition featured a tone that was introduced 10 seconds before inescapable shock was delivered through a floor grid. In the unsignaled shock condition the tone was distributed randomly throughout the session. Lymphocyte response to Con A was 34% lower in the unsignaled shock than in the signaled shock condition. The same trend was found for lymphocyte responses to pokeweed mitogen (PWM) and PHA, although results were not significant. These results suggest that psychological interventions involving prediction or control may lessen the influence of a stressor on immune function.

The influence of predictability was significant only when cells were challenged with Con A, whereas controllability affected response to PHA. Mormede et al. (1988) suggested that these differences in response to the mitogens may reflect a variation in the sensitivity of the response to the mitogens depending on the conditions implemented during the sessions. This could indicate a differential involvement of immune cells including T lymphocyte subsets, such as helper T cells versus suppressor/cytotoxic T cells.

Conclusions. Animal models are useful in examining stress and immune activity as many of the variables involved in an experiment may be better controlled (e.g., life history, diet, and living conditions). However, use of animal models in studying the relationships between cognitive and emotional variables and immunity is limited by several factors. It is difficult to examine many psychological variables in relation to stress and immunity in animals because there are no ways to tap the phenomenological aspects of their experience. Depression, loneliness, and anxiety are just a few of the psychological variables that may require self-reports from humans in order to distinguish them and to fully understand their relationship to stress and immunity. Although, there have been some animal paradigms that have been used as models of depression and anxiety (e.g., Estes & Skinner, 1941; Maier, 1984) and these models are useful tools in gaining an understanding these phenomena, they may only model particular aspects of affect or dysfunction. It has been suggested for example, that learned helplessness is a good model for depression (e.g., Seligman, 1975). However, others have suggested that although learned helplessness may tap into some aspects of depression it does not duplicate the full clinical phenomena of depression. Learned helplessness results from exposure to uncontrollable situations and leads to debilitated escape learning during subsequent events that may reflect behavior common during depression. Also, changes produced in lever-pressing activities of rats in the Estes and Skinner (1941) experiments may be associated with some of the properties of anxiety, but again may not represent definitive characteristics of anxiety in all situations. It would be difficult to use these models to measure levels of anxiety or depression during stress because they were developed to examine the mechanisms involved in formation of emotional disturbances and not as quantitative indices of them during stress.

Physiological and psychological differences between animals and humans make comparisons between the two groups difficult. Human coping skills, adaptation, and emotionality appear to be different from those of most animal species, and immune systems may function differently across species. For example, Laudenslager (1983) and Mormede et al. (1988) found a decrease in proliferation of lymphocytes to PHA and/or Con A associated with uncontrollable shock in rats, whereas opposite results have been found in humans (Weisse et al., 1990). It is therefore critical that research be conducted with human subjects if the ultimate goal is application to them.

Human Studies

Research on acute human stress responses and immune function has not generally been as common as has work with animals. To some extent, this is due to the greater ease of obtaining measures of immune response and of controlling for genetic and behavioral history. Despite this, some studies have begun to appear and since the 1980s, our knowledge of how people respond during stress has expanded dramatically. There are still relatively few studies of controlled acute laboratory stressors and immune function in humans, however. Most of the recent work has been correlational, comparing stress and immune responses of selected groups of people.

One study of acute stress considered task performance and exercise and examined several indices of immunity (Landmann et al., 1984). Changes in numbers of lymphocyte subsets were measured in response to a cognitive conflict task (a modified version of the Stroop task; Stroop, 1935) and after bicycle ergometry performed to submaximal work capacity. Mean numbers of granulocytes were significantly higher after exercise stress than at baseline and all lymphocyte subtypes were increased. Following the cognitive conflict task, numbers of monocytes, B cells and, natural killer (NK) cells were significantly higher. Cell numbers increased during both the cognitive conflict task and the bicycle ergometry, although the types of cells differed. However, failure to adequately separate the two stressors, our lack of knowledge of the time course of changes in lymphocyte subpopulations, and the fact that no control group was included in the study design make interpretation of these findings difficult.

In an attempt to better understand how rapidly immune system changes occur in the face of stress and to examine controllability of a stressor as a mediator between stress and immunity, Weisse and colleagues (1990) exposed subjects either to a controllable noise/shock stressor or an uncontrollable noise/shock stressor. Subjects in the controllable stressor condition had to learn how many times they needed to press a button in order to terminate the stressor. Subjects in the uncontrollable stressor group were yoked to this group and were unable to control the noise/shock regardless of how many times they pressed the button. In order to control for time and blood drawing procedures subjects also participated in a baseline session in which they were not exposed to stressors.

Immune activity was not significantly altered by uncontrollable stress although mood and task performance on an anagram task were in predicted directions. However, subjects in the controllable stressor group exhibited a significant decrease in lymphocyte proliferation to Con A as well as in percentages of monocytes at the end of the session. Although clearly establishing an association between stress and immune system change in humans under controlled laboratory conditions, these results are not consistent with those reported by Laudenslager (1983) and suggest that important differences between animals and humans may be involved. It may be that mechanisms involved in controllability of a stressor and its effect on immune activity in rats may not be the same as in humans. Alternatively, the time frame involved in this study may explain these different findings. In the Laudenslager (1983) study blood was collected from the rats 24 hours after stress exposure, whereas Weisse (1989) collected blood samples within 2 hours of the stressor. The length of time in sampling in the Laudenslager (1983) study may have led to observations of different immune changes or responses. If so, the time course of these effects needs to be established. Biphasic effects of stress modulation of immunity would suggest a far more complex relationship than has generally been assumed.

A second controlled laboratory study of stress and lymphocyte proliferation also provided evidence of acute stress effects on blastogenic outcomes and suggests that these changes may occur very quickly (Zakowski, McAllister, Deal, & Baum, 1991). The stressor was a 7-minute combat surgery videotape and a memory test requiring subjects to report on details of the film. This procedure was administered twice, using the same film and memory task. The control group participated in similar procedures but viewed a film of landscape scenes with calming music. Self-report measures of stress were supplemented by plasma cortisol measures and heart rate and blood pressure assessments before and throughout the tasks.

Lymphocyte proliferation to Con A (5ug/ml) was significantly lower among subjects engaged in stressful procedures than among control subjects, and differences in proliferation to Con A (10ug/ml) was in the same direction although not significant. There were no differences in response to challenge with PHA. Individuals in the experimental group who were labeled as high reactors because they exhibited the largest changes in systolic and diastolic blood pressures during the film also showed significantly less lymphocyte proliferation to Con A than did lower reactors or controls. There were again no significant differences in response to PHA.

Failure to find effects with PHA after finding them with Con A are consistent with Weisse and colleagues (1990) and Mormede et al.'s (1988) findings. Cortisol levels were not significantly different between the two groups nor were they related to immune function. Consequently, this study suggests that stress exposure may affect immune function and that individuals with greater sympathetic reactivity to a stressor in particular show larger decreases in immune function compared to those who are not as reactive.

Conclusions. To summarize, studies of animals have shown that there are changes in immune response following acute stressors such as shock, immobilization, territorial invasion, and exposure to a neutral stimulus previously paired with shock. Humans exposed to acute stressors also exhibit alterations in immune measures, although conditioned stress effects have not been demonstrated. These changes in immunity are presumably transient, although most studies have not followed responses for long enough periods to determine the actual duration of altered endocrine or immune responses. Psychological mediators such as the controllability or predictability of a stressor appear to buffer against the effect of stress on immunity in animals. However, controllability did not have similar effects in humans (Weisse et al., 1990). In addition, high reactors exhibiting larger changes in systolic and diastolic blood pressures during exposure to stressful procedures showed more stress-related deficits in lymphocyte proliferation than did lower reactors (Zakowski et al., 1991). This suggests that there may be physiological as well as psychological differences across individuals in response to stressful situations that may be related to changes in immunity, whereby some individuals react more dramatically to a stressor than others. The mechanisms involved should be investigated more fully.

CHRONIC STRESS AND IMMUNITY

As suggested earlier, chronic stress is a general category that covers a variety of types of events and reactions. Most studies of animals under chronic stress simply involve extending or increasing exposure to stressors used in studies of acute stress. In humans, however, such studies are exclusively naturalistic, considering independently applied stressors or persistent responses following shorter events. Consequently, the conditions under which these studies are done are not as controlled as are other studies, but potential applicability and significance for health may be greater.

Animal Studies

Research on chronic stress and immune function in animals must consider several potential barriers, including the effects of rapidly aging animals, habituation, and illness. Ghoneum, Gill, Assanah, and Stevens (1987) suggested that old rats subjected to stress have larger decreases in splenic and peripheral blood NK activity compared to young rats and this may be a factor in hesitancy of researchers to examine chronic stress in animals: Chronic stress studies may be impractical because animals of choice for these studies tend to age rapidly. However, if completed before the animal has reached "old age," studies lasting a period of months rather than a year or longer, depending on the species of animal may be feasible. If the studies are begun while the animal is still relatively young the effects of age may be avoided or controlled as well.

As we have suggested, acute stressors appear to suppress immune function. Some investigators, however, have argued that prolonged stressors (a month or longer) may increase functional indicators such as cell proliferation. Monjan and Collector (1977) examined the effects of a noise stressor over time and its relationship with immune function. In the experimental group, mice were subjected to 100 db of broad band sound for 5 seconds every minute for 3 hours a night. Animals varied in how many days they were exposed to the noise, up to 39 days. At the same time, control animals were subjected only to the normal activity of the animal room. In vitro lipopolysaccharide (LPS) was used to stimulate splenic B cell function and Con A was used to stimulate T cells. Also, T cell function was assessed by the lysis of P815 target cells in vitro. Exposure to the noise of 2 weeks or less was associated with lower lymphocyte proliferation to LPS and to Con A than was exposure to control conditions. Longer term exposure to noise (2–4 weeks) appeared to increase lymphocyte proliferation. Suppression of immune activity seemed to occur initially with shorter term noise stress, but gradually recovered and eventually exceeded original baseline levels with longer exposures, resulting in an apparent enhancement effect.

In an effort to explain the differential effect of the stressor on immunity over time, Monjon and Collector (1977) argued that animals exposed to noise stressors for more than 10 days are able to adapt and this adaptation is associated with reduced glucocorticoid levels, whereas acute stress increases levels of glucocorticoids, which presumably suppress immunologic responses. However, glucocorticoid levels were not associated with immunoenhancement following prolonged sound exposure. Riley (1981) also argued that these results were due to adaptation; animals were able to adjust to the stressor, gradually recovering function and briefly extending above baseline as normal responses were restored. Similarly, Borysenko and Borysenko (1982) suggested that the nature of the stressor, its duration, and the amount of time between the stress and immune measures may affect whether augmentation or suppression of immune activity is found. They noted that the findings in the Monjan and Collector study (1977) could have been due to rebound overshoot. Therefore, enhancement may not be due to prolonging the sound stressor but rather is a function of how long after exposure to a stressor immune measures are taken and whether adaptation is achieved.

Because there are so few animal studies examining chronic stress and immune activity it is difficult to assume that all forms of chronic stress would affect animals similarly. Because animal models are an important tool with which to examine immunity, the issue of whether different chronic stressors effect immune function similarly in animals must be addressed so that chronic stress and immunity can be better understood. Evidence that animals do not always adapt to chronic stressors or show apparent enhancement over time is provided by a study of 6-month stressor exposure, measuring immune function in rats undergoing escapable electric footshock (Odio, Goliszek, Brodish, & Ricardo, 1986). Four groups of 4-month-old male rats were used in the study. The stressor involved a variable interval schedule that shifted electrification from one half of the cage floor to the other. A tone was presented 1 second before each shift. Group I, the control group, received no shocks. Group II received 14 hours of shock exposure per week (2 hours of stress each day). Group III was exposed to 20 hours of stress per week with 4 hours of stress each day for 5 days each week. Group IV was exposed to 28 hours of stress per week with 4 hours of stress each day. These schedules were maintained for 6 months and animals received from 0 to 700 hours of shock exposure. One month after the last stress session the animals were sacrificed and their splenic lymphocytes examined.

All animals exposed to the stressor exhibited decreases in immune function. Exposure to long-term chronic stress resulted in a decrease in T lymphocyte proliferation to Con A and PHA even beyond the period of shock administration. Animals receiving only 14 hours of stress per week exhibited only moderate immunosuppression compared to other groups. Animals exposed to 20 or 28 hours of stress per week showed a 40% decrease in proliferative activities compared to controls.

These results suggest that immune system responses to stress are related to the amount of stressor exposure involved. That the suppression of immune function may extend beyond the time of the stressor application is also of interest. Monjan and Collector (1977) found that lymphocyte proliferation to Con A and LPS increased with long-term exposure to noise, but these measures were taken on the same day as the termination of the stressor, and it is difficult to reconcile the possible effects of a stressor on immune function at a later time with these results. The time course of immune system changes following a stressor still needs to be determined. Also, a dose response relationship may be important in the immune system's adaptation to a stressor. High stressor levels over time may continue to blunt immune activities and inhibit adaptation, whereas stressor levels in the Monjan and Collector study (1977) may not have been as resistant to adaptation and an overshoot in immune activity may have resulted.

Chronic stress in animals may also be associated with tumor growth. The ability of a tumor to develop is thought to be related to immune function by way of immune surveillance systems and therefore, effects of stress on immune function may be indirectly related to cancer progression. In a study by Riley (1975) stress-related tumor incidence in female mice infected with nodule-inducing virus was examined. Two groups of female rats (Groups A and B) who were infected with mammary tumor virus (MTV) were housed with males in standard stainless steel box cages. A third group (C) was infected with MTV and was housed without males, in plastic cages under protective conditions. A fourth group (D) was not infected with MTV and was randomly assigned housing with or without males in plastic cages under protective conditions. However, because all D subgroups had similar incidences of tumors, data on the subgroups were not given separately. Females in Groups A and B were exposed to handling, dust, odor, noise, and pheromones because they were housed in open racks. Females in Groups A, B, and C were handled weekly for tumor inspection and were frequently bled. In addition, females in Group A had one or more litters. Group C, however, was housed in plastic cages within ventilated shelves that protected them from environmental stress factors, although they were frequently weighed, inspected for tumors, and bled. Riley (1975) suggested that they experienced a moderate amount of stress compared to Groups A and B. Group D was thought to have experienced little or no stress as they also were housed in enclosed ventilated shelves and were rarely handled or bled.

Group A exhibited significantly earlier tumor appearance than did other groups with a median latent period of 276 days. Animals in Group B had a median latent period of 358 days, whereas animals in Group C had a median latent period of 566 days, significantly greater than Groups A and B. Animals in Group D still had no tumors at 400 days and their median latent period was greater than 800 days. Clearly, a dose response effect similar to that reported by Odio et al., (1986) indicated that increased stress was associated with greater tumor production or an inhibition of tumor rejection. Riley (1975) argued that although the milk-transmitted oncogenic Bittner mammary tumor virus is present in these mice from the time they are born, as long as immunologic surveillance systems are functioning properly the cells that are transformed and become malignant are recognized and destroyed. Under stressful conditions an increase in mammary tumor virus production may occur in the context of decreases in immunological control of malignant cells.

In another series of studies, Riley (1981) used rotation on a modified turntable as a stressor and examined lysis of lymphocytes, disintegration of the thymus and tumor growth in mice. The turntable was designed so that an entire cage of animals could be rotated without exposing animals to a novel environment or changing the availability of food and water. Following a rotation schedule of 10 minutes each hour at 45 rev/min over a 5-hour time period, substantial leukocytopenia was observed. Circulating lymphocyte damage occurred within 1 to 2 hours. Thymus involution followed, occurring within 24 hours. Riley (1981) suggested that because most of the circulating leukocytes lost were T cells and additional damage to the thymus could delay replacement, there was a significant effect on T cell-mediated immunity. In a subsequent study, half of a population of mice subcutaneously implanted with 6C3HED lymphosarcoma tumors were rotated at 45 rev/min for 10 minutes out of each hour for 3 days (Riley, 1981). Tumor growth was greater after 30 days among stressed mice compared to control animals. Decreased immunocompetency in the stressed mice may have resulted from the stress caused by the rotation, allowing increased tumor growth.

Conclusions. Acute stressor exposure among animals has been associated with suppressed immune function, but responses to chronic stressors may be more complicated. In some cases, animal immune systems appeared to adapt to prolonged stressors over time, whereas in other situations their immune functions remained suppressed. There have been a variety of explanations for this discrepancy. The ability to adjust to stressors may depend on the nature of the stressor and/or its duration. In addition, immune system responses may be related to the amount of stressor exposure involved, where a dose response relationship may be important in adaptation or resistance to adaptation.

In some chronic stress studies it was observed that the administration of chronic stressors resulted in immune response changes that lasted longer than the presence of the stressor. However, not all studies measured immune responses beyond stressor administration and therefore conclusions cannot be made whether this phenomenon is always present. The time course of immune function changes needs to be further investigated.

In examining chronic stress and its affect on health, tumor growth was also found to correspond with chronic stressor administration. It has been suggested that tumor growth may be related to immunological control of malignant cells and therefore, the effects of stress on immunity may be related indirectly to cancer progression.

Human Studies

Many studies have investigated long-term stressors (either those of an intermediate duration or very long duration) in humans since the mid-1980s. Many have studied groups of students taking examinations (during semester midterms or finals) or a single major exam. We refer to these as *intermediate* because the period of threat or distress associated with an upcoming exam may last for a number of weeks, changing in stressfulness as exam time draws closer. However, these stressors may not have response durations as long as other stressors that last for months or years.

Intermediate Stress. A study conducted in Norway (Halvorsen & Vassend, 1987) considered undergraduates majoring in psychology who were required to take written exams for 2 days. Immune system activity was measured 6 weeks before the exams, 1 day before the exams, and 12–14 days after the examination. A group of students not taking exams served as controls. The State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) was also administered on the days that immune measures were taken.

State anxiety increased significantly just before the exams, as did numbers of circulating monocytes compared to controls during the same time period and as compared to themselves 2 weeks later. However, the fraction of large helper/inducer T cells (larger cells indicate cell activation) was reduced just before the examination compared with 6 weeks before and 2 weeks after. The fraction of suppressor/cytotoxic T cells was also significantly reduced compared to 2 weeks after but was not significantly reduced when compared to rates obtained 6 weeks before. No differences in fractions were found in small (presumably inactive) cells.

It is possible that stress inhibited activation of these cells or, as Halvorsen and Vassend (1987) suggested, activated T cells are more strongly affected by stress than are inactive cells. That stress may inhibit activation is supported by the finding that the percentages of cells expressing IL-2 receptors was also reduced just before examinations. A delayed effect was also observed; a reduction in proliferation of T cells exposed to PHA, antigen (D. farinae), and pooled lymphocytes 2 weeks after the exams was found despite only a minimal nonsignificant reduction just before the examination period. This may have been due to an oral exam that students were scheduled to take shortly after the last blood draw but could have reflected long-term effects of the first set of exams. When these cells were cultured with IL-2 fortified medium, however, there was significantly less proliferation of T cells during the exam period compared to 6 weeks before.

In a study by Workman and La Via (1987), the effects of stress on T cell proliferation was examined in 15 medical students taking the National Board Medical Examinations. Blood drawing and questionnaire administration occurred the day before, and 1, 4, and 6 weeks after the exam. Fifteen age- and gender-matched controls also participated in the study. The Impact of Events Scale (IES; Horowitz, Wilner, & Alvarez, 1979) was used to measure overall stress as well as stress response styles in all of the subjects. The IES subscales include *avoidance,* made up of items assessing the extent in which a person attempts to avoid reminders of stressors (e.g., avoiding talking or thinking about the stressor) and *intrusion,* containing items that measure the extent to which a stressor intrudes into a persons thoughts, dreams, and so on. The Social Readjustment Rating Scale (SRRS) was also given to all subjects to measure life event stress during the previous 6 months.

Total scores for the IES were significantly higher for the experimental group than the control group the day before the examination but were not different after the exam. Students taking exams also exhibited significantly less T lymphocyte proliferation to PHA on the before the exams, and those with higher intrusion scores had the lowest T cell proliferation to PHA. A week later, students who had taken exams still showed significantly smaller proliferative responses to PHA mitogen compared to the control group. Partial recovery was observed after 4 weeks; T cell proliferative responses were significantly higher than they had been at 1 week after the examination but were still significantly lower than measures taken before the exam. At 6 weeks postexamination T cell responses were no longer different from preboard measurements, suggesting that it took about 6 weeks for immune function to return to normal after the stressor. The evidence for this recovery period is not definitive, however, as intervening conditions were not assessed following exams.

Kiecolt-Glaser, Glaser, and their colleagues have conducted several studies of medical students' immune function, and exam stress (Glaser, Kiecolt-Glaser, Stout, Tarr, Speicher, & Holliday, et al., 1985; Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986; Glaser et al., 1987; Kiecolt-Glaser et al., 1984; Kiecolt-Glaser et al., 1986). Differences in NK activity have been observed during final examinations among medical students compared with measures taken 1 month before the exams (Kiecolt-Glaser, Garner, et al., 1984). Similarly, differences in numbers of NK cells, percentages of helper T cells, differences in lymphocyte proliferation to a mitogen challenge, and antibody titers to Epstein Barr virus (EBV) between examination and nonexamination periods have been reported (Glaser, Kiecolt-Glaser, Speicher, & Holliday, et al., 1985; Glaser et al., 1986; Kiecolt-Glaser et al., 1986). The EBV is used as a measure of cellular immune activity and cellular control over a latent virus (Glaser et al., 1987) and therefore, an inhibition of immune mechanisms that normally suppresses the virus may result in the increase of antibody titers to that virus.

Another study by this research team yielded some important evidence of immunological effects of psychological distress at the molecular level (Kiecolt-Glaser, Stephens, Lipetz, Speicher, & Glaser, 1985). The critical process of DNA repair in lymphocytes exposed to X-irradiation (in vitro) was examined in nonpsychotic psychiatric inpatients who had been divided into high- and low-distress subgroups according to measures on the Minnesota Multiphasic Personality Inventory (MMPI) Depression Scale 2. Significant differences were found in DNA repair between the high- and low-distress groups, with the high-distress group exhibiting significantly less DNA repair after 5 hours than the low-distress group. Kiecolt-Glaser and her colleagues (1985) suggested that this poor DNA repair may contribute to pathogenesis because faulty DNA repair may be related to increased occurrence of cancer. A concomitant decrease in NK cell activity with increased distress, as found in studies of examination stress in medical students, could result in markedly poorer destruction of transformed cells.

Psychosocial Mediators. Studies examining the effects of stress on immune activity in humans have also reported data supporting the idea that psychological mediators may magnify or moderate responses to a stressor. For example in studies of medical students during and after exams, lonelier students had significantly higher antibody titers to EBV than did less lonely students. Loneliness also appeared to affect immune function in psychiatric inpatients; those scoring above the median on the UCLA Loneliness Scale

(Russell, Peplau, & Cutrona, 1980) had significantly lower NK activity and depressed T lymphocyte proliferation to PHA compared to those in the low loneliness group (Kiecolt-Glaser, 1984).

One important strength of the program of research by Kiecolt-Glaser, Glaser, and their colleagues is the demonstration that interventions to reduce distress block stress-related decreases in immune indicators or enhance them. Perhaps the clearest way to demonstrate that stress affects immunity is to reduce stress and measure simultaneous changes in immune function. One study examined the influence of relaxation techniques as a buffer from the stress of examinations in first-year medical students (Kiecolt-Glaser, Ricker, et al., 1986). Blood samples were collected 1 month before the examinations and again during the examination period. Half of the subjects received hypnotic/relaxation training during the interval between blood draws. Changes in distress levels were measured as were NK activity and lymphocyte subpopulations.

The two groups showed no significant differences before treatment on immunological measures or in self-reported distress. Further, there were no significant changes within the relaxation training group across the examination period. Subjects not learning relaxation, however, exhibited significant increases in anxiety and distress during the examination period. Although both groups showed a significant decrease in NK cell activity and percentages of helper/inducer cells during the examination period, the frequency of use of relaxation techniques was associated with percentages of helper/inducer cells during examinations.

A clearer instance of stress reduction and buffering of associated immune system changes was provided by a study of older people drawn from a geriatric population (Kiecolt-Glaser et al., 1985). The relaxation group in this study displayed a general increase in the T lymphocyte response to PHA, a significant increase in natural killer cell activity and a significant decrease in antibody titers to Herpes siplex virus compared to controls. Relaxation training was also associated with decreases in measures of distress.

Marital quality and separation/divorce can be considered more chronic than examination stress and have been studied as factors affecting immunity. Thirty-eight married women and 38 separated or divorced women who had been separated or divorced for 6 years or less participated in one study (Kiecolt-Glaser, Fisher, et al., 1987). The two groups were matched for age, socioeconomic status of the (ex)husband, education, number of children, and length of marriage. The results of the study indicated that poorer marital quality was related to higher levels of depression and lower T lymphocyte proliferation to Con A and PHA as well as an increase in antibody titers to EBV. More recent marital separation (1 year or less) and greater attachment to the (ex)husband lead to increased depressive symptoms and lower helper T lymphocytes and helper–suppressor ratios compared to the married controls. Also, the length of separation was significantly and positively related to lymphocyte response to PHA. Women who had been separated for 1 year or less also had significantly higher antibody titers to EBV and a significantly lower percentage of NH cells than did married women. Similar findings have been reported for divorced or separated men (Kiecolt-Glaser et al., 1988).

Chronic Stress. Among the first prospective studies of immune function in relatively healthy people were studies of bereaved spouses. One, reported by Bartrop, Lazarus, Luckhurst, Kiloh, & Penny (1977), involved 26 surviving spouses, recruited for the study along with 26 control subjects who were matched for age, gender, and race. The first blood samples were taken within 3 weeks after the death of their loved one and the second were taken 6 weeks later. Control subjects had their blood drawn at the same times with assays performed on both groups simultaneously. Bereaved subjects exhibited significantly less lymphocyte transformation to PHA (at 10 and 20 ug/ml) and Con A (at 5 and 50 ug/ml) 6 weeks after the loss than did controls. Proliferation of cells to Con A challenge (at 5 and 50 ug/ml) was significantly lower 6 weeks after the loss than 3 weeks after among bereaved individuals, suggesting that lymphocyte proliferation to mitogens decreases over the first 6 weeks of bereavement rather than diminishing all at once and recovering slowly.

A prospective study of 15 husbands of women with advanced breast cancer also provided evidence of bereavement-induced immune system changes (Schleifer, Keller, Bond, Cohen, & Stein, et al., 1983). Prebreavement immune levels were compared to those after the death of a spouse. The number of T and B cells were not significantly different, but lymphocyte proliferation to Con A, PHA, and PWM were lower during the first 2 months of bereavement compared to before the death of their spouses. During the follow-up period of 4 and 14 months postbereavement lymphocyte stimulation responses were intermediate between before the spouses' death and during the first 2 months postbereavement. This study, however, did not include control subjects and therefore the pre- and postbereavement timepoints cannot be compared to individuals not experiencing the death of a loved one. Also, as the investigators note, a larger sample may be necessary to ascertain whether the responses observed during the follow-up periods exemplify subgroups, with some individuals exhibiting a recovery of lymphocyte responses and others having lower immune responses at later time points. Finally, depression and loneliness were not measured in the study, although these variables would be expected to be relevant during bereavement.

The role of depression in modulating immune function during bereavement appears to be important. In a study of bereaved women, Irwin, Daniels, Smith, Bloom, and Weiner (1987) measured NK cell activity and depressive symptoms at weekly intervals 1 to 2 months before the death of the husband and at least twice during the month following the spouses' deaths. Neither NK activity nor depression scores were significantly different from anticipatory to post-death bereavement periods. This may be due to the stress of anticipatory bereavement, which may also provide valuable time for coping and decrease the eventual impact of death. However, increases in depressive symptoms from before the death of the husband to after led to decreases in NK cell activity.

Recently, Stein (1989) has suggested that immune system changes may not be specific to depression but rather to subgroups of depressed individuals. It was proposed that altered immune measures may be present particularly in elderly, severely depressed individuals. Immune function in patients with major depressive disorder who were drug free, hospitalized, and ambulatory was examined (Schleifer et al., 1989). The patient sample consisted of a range of ages, gender, and illness severity. Depressed patients and age- and gender-matched controls showed no significant differences in the number of T and B lymphocytes, T4 or T8 cells, lymphocyte proliferation to PWM, Con A, and PHA, and NK cell activity. However, multiple regression analyses examining the contribution or age, severity of depression, gender, and hospitalization to immune status revealed that there were significant age-associated differences between depressed individuals and controls in number of T4 lymphocytes and in mitogen-induced lymphocyte activation. Similarly, severity of depression was significantly related to alterations in immune measures.

Very long-term stress and immunity have also been examined among family caregivers of Alzheimer's disease (AD) victims (Kiecolt-Glaser, Glaser, et al., 1987). The AD-afflicted individuals had been diagnosed for a mean of 2.83 years with some newly diagnosed and others diagnosed up to 11 years before, and stress associated with caring for these individuals may have continued for quite some time. Half of the subjects lived with the AD victim, 10 AD victims were in nursing homes, and 7 AD victims lived alone or with another relative. Control subjects were also studied; they were not caregivers of AD patients but were matched with the caregivers for age, years of education, and family income. Subjects' depressive symptoms were measured, as well as patterns of social contact, AD patient history, and current functioning information.

Caregivers exhibited significantly higher levels of depressive symptoms than did control subjects. Greater impairment of the AD patient was also associated with fewer social contacts by the caregiver. Significantly higher antibody titers to EBV and lower percentages of total T lymphocytes and helper T lymphocytes were found in caregivers compared to controls.

However, there were not significant differences in the percentages of suppressor T cells and NK cells. Caregivers who belonged to a social support group were also compared to those who did not and group members rated themselves as significantly less lonely and had a significantly larger percentage of NK cells than those who did not participate in a group.

In another study that measured very long chronic stress, people living near the Three Mile Island (TMI) nuclear power plant were compared to individuals living about 80 miles away (McKinnon, Weisse, Reynolds, Bowles, and Baum, 1989). The study was conducted more than 6 years after the accident at TMI and psychophysiological data collected over this 6-year period yielded evidence of continuing stress among residents of the TMI area (e.g., increased symptom reporting, elevated resting blood pressure, and catecholamine levels relative to controls). Individuals living near TMI also had significantly lower numbers of B lymphocytes, NK cells, and T-suppressor/cytotoxic lymphocytes compared to control subjects, and exhibited significantly greater antibody titers for herpes simplex virus and cytomeglavirus, both latent viruses, and no differences in titers for rubella virus, which is not latent. These data suggested that stress associated with the TMI accident and its aftermath may have suppressed key elements of the immune system, although possible radiation effects could not be evaluated.

Conclusions. Animal studies have suggested that long-term stressors may decrease immune function or increase it above original baseline levels. If one allows for adaptation, other studies have found that animals exposed to long-term stressors exhibit decreases in immune function associated with the amount of stressor exposure. Over time, high stressor levels may continue to inhibit immune responses and lessen the ability to adapt, whereas lower stressor levels may be conducive to adaptation. Chronic stress has also been associated with tumor growth in mice (Riley, 1975, 1981), and is thought to be related to immune surveillance systems.

In humans, chronic stressors of an intermediate duration such as examination stress appear to affect immune function, including reducing numbers of large helper/inducer T cells, fractions of suppressor/cytotoxic T cells, proliferation of T cells to PHA, numbers of NK cells and their activity, and increasing antibody titers to EBV. Psychological mediators such as anxiety, loneliness, and intrusive thoughts may further affect immune function responses to stressors and interventions such as relaxation may buffer against stress and lessen the effects of stress on immune function.

Long-term chronic stressors such as separation/divorce or bereavement also appear to affect immunity. Differences between chronic stress and control groups in numbers of helper T lymphocytes, the fraction of