within these cells that are also activated by cytokines. The obvious implication is that neurotransmitters may modulate the effects of cytokines. In fact, there is evidence that this is the case. The effect of IL-2 in stimulating killing activity in LAK (lymphokine activated killer) cells is greatly potentiated by somatostatin and β-endorphin, even though these neurotransmitters have no effect in the absence of IL-2.[20]

Furthermore, cytokines themselves may act on the nervous system, either at the level of the CNS, or possibly directly on nerve terminals in their environment. Recent investigations of cytokine influences on neuronal activity suggest that immunization with antigen or IL-1 can influence NE release and turnover in both the CNS and in peripheral lymphoid organs.[21] The mechanism of this interaction is unclear at present. It is not known whether NA neurons, either in the CNS or in the periphery, possess receptors for IL-1 or other cytokines. However, the existence of such feedback loops serves to integrate the activities of nervous system and immune system even further. CIN

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Modulation of the Cellular Immune Response by Stress

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There are now conclusive data from both animal and human studies that the immune system is integrated in an axis which includes the endocrine system and the central nervous system (CNS).[1,17,40,41] The complex interactions among these three systems has been studied not only with respect to learning the mechanisms underlying these interactions, but also to explore the health implications of these interactions. We can explain in part the communication between the CNS and the immune systems through modulation of the endocrine system and by neuropeptides. There is

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now also evidence to support the possibility that there may be important interactions between the CNS and specific subsets of lymphocytes as demonstrated by the direct contact of nerve endings with T lymphocytes in spleens of rats.[8,9]

The communication between the CNS and immune systems is not unidirectional, but is functionally a feedback loop from the immune system to the CNS. One example of this feedback loop is Interleukin-1 (IL-1) which is produced by macrophages. IL-1 has the ability to affect hypothalamic activity, thereby promoting corticotropin releasing factor (CRF) secretion and adrenocorticotropic hormone (ACTH) stimulation.[36] This interaction in turn stimulates the production and secretion of cortisol; glucocorticoids are known to have immunoregulatory activities across a broad spectrum of the cellular immune response.[11,22,32,33,39]

There is now an extensive literature on stressful life events that suggests that individuals who have experienced recent major negative life changes may be at greater risk for illnesses, particularly infectious disease and perhaps malignant disease. In general, however, the correlations are not large and account for perhaps 10% of the variance.[6] However, within this limitation the effects are remarkably consistent when one studies different populations and different kinds of life events. The influence of psychological stressors on general health has been explored in a number of groups. One example is the immunological and pathological consequences of one of the most extremely stressful life events, the death of a spouse. It has been shown in a number of studies that widowed survivors experience an increased risk of morbidity and mortality following the death of their spouses.[3,42] Other studies have shown in the same group that there are impairments in certain aspects of the cellular immune response, suggesting that the changes in immune competence associated with the psychological stressor may play a role in increasing the risk for illness.[38]

Academic Stress as a Model for Commonplace Stressors

Work from our laboratory has been directed toward exploring the possibility that relatively commonplace stressful events might be associated with the suppression of the immune response and whether the suppression could have implications for risk for infectious diseases such as upper respiratory track infections. To explore this hypothesis, we have performed several studies involving first and second-year medical students enrolled at the Ohio State University College of Medicine, using a cyclical academic stress model to explore this relationship. This group provided an excellent sample to study the effects of an acute cyclical stressor, since the medical school curriculum is designed so the students have several 2- or 3-day examination blocks throughout the academic year. Therefore, as a class they either cycle together through examination periods, a time associated generally with higher levels of acute stress, or they do not. The experimental design is a within-subjects design with the medical students acting as their own control as they are followed over the academic year.

Peripheral blood leukocytes (PBLs) were obtained during examination blocks that had been demonstrated to be high periods of psychological distress as well as 1 month prior to the examination block, a time designated as baseline.[25] In our first study we found a decline in natural killer (NK) cell activity (using K562 cells as target cells) in PBLs obtained from 75 medical students during final examinations, as compared to NK cell activity in blood samples obtained at the baseline. We also found that psychological distress was increased at the time of examinations.[25] In a follow-up study we found similar decreases of NK cell activity using a different target cell (MOLT4), and simultaneously found a decrease in the number of NK cells using two independent measures, the number of large granular lymphocytes, the NK cell phenotype, and the number of cells expressing an NK antigen detected with the leu-7 monoclonal antibody.[15,25]

The ability of PBLs obtained from medical students to proliferate after being stimulated with the T-cell mitogens concanavalin-A (Con-A) and phytohemagglutinin (PHA) was also shown to be down-regulated during the period of examinations.[28] In two separate studies, the PBLs obtained from the medical students at the time of examinations when stimulated with Con-A were also significantly inhibited in their ability to synthesize gamma interferon.[14,15]

In a recent study, we explored the expression of the Interleukin-2 receptor (IL-2R) and the synthesis of IL-2R mRNA by PBLs obtained from the medical students at the time of their examinations.[12] In three separate studies, the PBLs obtained at low baseline periods had significantly higher percentages of IL-2R positive cells after mitogen stimulation, as compared to PBLs obtained from the same individuals during examinations. In addition, in one study the level of IL-2R mRNA in PBLs obtained during examination periods was found to be significantly lower than mRNA levels in PBLs obtained at the baseline period; this corresponded with a decrease in IL-2R expression. When the same cell cultures were assayed for IL-2 production, higher levels were found in the supernatants of the Con-A stimulated PBLs from the examination blood sample than the PBLs obtained at baseline. It is possible that the accumulation of IL-2 in the supernatants in this PBL sample may have been due to the down-regulation of IL-2Rs and therefore reflects, to some degree, an accumulation of IL-2 not bound to the IL-2Rs. Whatever the reason, the presence of increased accumulation of IL-2 in this study suggests that IL-2-induced up-regulation of IL-2R expression is not sufficient to overcome the stress-induced inhibition of IL-2R expression; IL-2 is involved in the regulation of IL-2R expression, since studies have shown that addition of IL-2 to mitogen stimulated PBLs augments IL-2R expression.[7,34] The data, however, are consistent with the fact that IL-2 and IL-2R synthesis are controlled by different regulatory cascades.[19,20,31,43]

It is known that the immune response can be affected by poor nutrition. In the studies described in this review, nutrition has been controlled for by the measurement of plasma albumin and transferrin levels which provide good indicators of protein intake.[5] In all studies, both albumin and transferrin levels were within

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normal ranges. Therefore, the changes in cellular immune response that we observed were probably not a function of nutritional deficits.

In addition, other factors such as alcohol and caffeine intake, drug use, smoking, sleep and weight changes were also evaluated in the data analysis. While changes were observed in one or more of these factors, none was correlated with the immune changes observed.[13,14,25–29]

The Impact of Psychological Stress on Herpes-Virus Latency

It is known that the changes in antibody titers to latent herpes viruses may reflect changes in cellular immune competence.[18] Elevated antibody titers to one or more of the latent herpesviruses are generally thought to occur as a result of the down-regulation of the cellular immune response with the resulting reactivation of the latent virus. This is generally common, for example, in patients with immunosuppressive diseases such as AIDS or individuals who are getting immunosuppressive therapies such as radiation therapy.

In these studies, we have measured antibody titers to three latent herpesviruses: Epstein-Barr virus (EBV), Herpes simplex virus type 1 (HSV-1), and cytomegalovirus (CMV). We found significant changes in antibody titers to EBV virus capsid antigen (VCA IgG) in several studies.[13,14,24,30] Similar changes to HSV-1 and CMV, but not poliovirus type 2, were also observed.[13] In one study we found that concomitant with the increases in EBV antibody titers was a decrease in specific T-cell killing of the outgrowth of EBV infected/transformed autologous B-lymphocytes obtained from the medical students. We further found that there was a decrease in the synthesis of a leukocyte migration inhibition factor (LIF), which is expressed during the recrudescence of HSV-2 infections.[14] The relationship between HSV reactivation and decreased LIF production in this medical student group is consistent with earlier findings that linked recrudescence with LIF activity in patients with genital herpes infections.[37] These data, as well as the changes in cellular immune response, are reviewed in Bonneau, et al., 1990; Kiecolt-Glaser and Glaser, 1990.[4,27]

Of interest is a clinical study by Kasl, et al.,[21] who obtained psychological data and EBV antibody titers of West Point cadets who were seronegative for EBV, and therefore not latently infected with the virus, prior to entering West Point. Over a 4 year study, the data showed that there was a triad of psychosocial risk factors (high levels of motivation for military career, poor academic performance, and having a father who was an "overachiever") which were associated with three illness indices. These indices included risk for seroconversion to EBV, a longer hospitalization in the infirmary following seroconversion, and higher antibody titers to EBV in those who did seroconvert in the absence of clinical symptoms.

In two other studies it was demonstrated that higher EBV antibody titers to early antigen (EA) and VCA, two antigens associated with virus replication, were found in patients who were depressed and with previous diagnosis of mood and/or personality disorders.[2,10] In another study, it was demonstrated that there is evidence showing an association among psychological stress, HSV-2 lesions, and $CD8^+$ T-lymphocytes.[23] Finally, evidence from our laboratory has shown the impact of age on the ability of the immune response (presumably the cellular immune response) to maintain and control latent EBV. We found that there was significantly higher EA IgG, VCA IgG, and VCA IgA antibody titers in an older but otherwise healthy population with a mean age of 70 as compared to medical students.[16] We also found that there was a significantly higher percentage of VCA IgA positive individuals in the geriatric group as well. These data are all consistent with the hypothesis that different psychological stressors or an aging immune response, either of which can modulate the cellular immune response, can have impact on the ability to control the expression of latent herpes viruses. Whether the direct impact of hormones such as glucocorticoids on the reactivation of these viruses is part of this interaction is still an open question and needs to be explored.

Health Implications

It is hypothesized that the immunological alterations observed in these studies are at least in part a consequence of distress-related changes in endocrine function.[1,33] While it is known that significant alterations in the cellular immune response is associated with greater morbidity and mortality in AIDS patients, for example, the actual health consequences of moderate or small changes in the cellular immune response is less clear. Little is also known of the kinetics of the immune response in relationship to disease risk.

There are a number of studies that have shown that individuals who have experienced major negative life events are at a greater risk for a variety of illnesses. For example, separated, divorced, and widowed individuals have greater morbidity and mortality than similar married individuals; the greatest risk for illness is associated with separation and divorce, not bereavement.[3,42] Work from our laboratory studying similar populations has demonstrated that decrements in certain aspects of the cellular immune response are consistent with these clinical findings.[30]

As already discussed, there is good evidence that the medical students in our studies are experiencing modulation of their cellular immune response associated with taking examinations. The fact that these students also self-reported a higher incidence of infectious disease symptoms, particularly symptoms associated with upper respiratory tract infections like colds and flu during the examination periods, suggests that there is possibly a link between stress-related immunosuppression and health in this population.[14]

Although the data obtained in these studies are consistent with epidemiological data that suggest that more distressed populations have significantly higher rates of morbidity and mortality, it should be emphasized that there are a number of behavioral differences that may contribute to the observed epidemiological differences in risk. In the case of marital disruption, it has been suggested that non-married individuals may have riskier life styles than married persons. For example, they may drink, use drugs, have

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poorer nutrition than their married counterparts.[42] In all the studies reported from our laboratory, we have excluded subjects who have reported drug or alcohol abuse. Weight, sleep, and nutrition, as already discussed, are also variables that are also carefully considered in evaluating the immunological changes. While it is likely that distress-related behaviors probably contributed to the morbidity and mortality observed in epidemiologic studies, the data from our studies suggest that there may be important immunological differences in individuals who do not differ on obvious health-related variables.

On the whole, we would speculate that the stress-related immunosuppression may have its most important health consequences in those individuals whose immune function is already impaired before the onset of the stressor. In such individuals, there may be a further downward change in the immune response, resulting in a response that falls into a range where health effects might be more profound particularly after exposure to an infectious agent. One group for which this may be particularly important is older adults, where there have already been shown to have reliable age-related decrements in cellular immunity. In support of this hypothesis is the fact that poorer cellular immune function is associated with greater mortality in individuals over 80 years of age.[35] Another such risk group might be in patients with immunosuppressive diseases such as AIDS.[26] In these high risk groups, emotional distress may affect morbidity and mortality in ways yet to be explored. CIN

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Effects of Neuropeptides on Cells of the Immune System

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Recently, there has been considerable interest in the intercommunication between the nervous system and the immune system.[2,18] Speculations and investigations of the effects of the nervous system on immune function have largely focused on glucocorticoids and catecholamines,[18] but there has also been some interest in the effects of neuropeptides, especially the endorphins, and other peptides found in autonomic terminals, such as substance P (SP), and vasoactive intestinal polypeptide (VIP). This interest has been enhanced by the observations of Blalock's group[7] and others that cells of the immune system can synthesize and secrete peptides in small quantities. Whether or not such peptides can be secreted in sufficient quantities to have classical endocrine or other systemic effects is controversial.[19,87] However, it is possible that secretion of peptides within an organ such as the spleen, thymus, or the lymph nodes may achieve sufficient concentrations that local changes of immune function are possible. Indeed, such a mechanism would provide the opportunity to regulate immune responses (eg, the inflammatory response) in a more specific way than by increasing circulating concentrations of the hormones. These effects of peptides could then locally counteract the rather unimodal immunosuppression elicited by glucocorticoids.

This review will attempt to summarize the complex and frequently conflicting effects reported of neuropeptides on immune cells both in vivo and in vitro.

Opioid Peptides (Endorphins)

Several authors have reviewed the effects of endorphins on immune cells.[72,84] Many studies have indicated the presence of opiate binding sites on human polymorphonuclear leukocytes, lymphocytes, phagocytes, and platelets using various radioligands, such as dihydromorphine, naloxone, β-endorphin (βE), methionine-enkephalin (ME), and leucine-enkephalin (LE).[84] Only one report found no opiate receptors on human mononuclear cells using naloxone and D-ala-D-leu-enkephalin as radioligands.[54] The different endorphins display different specificities towards different types of opiate receptors, μ, κ, δ and ϵ, and clearly the most useful data will be obtained from specific ligands for the various subtypes. However, as will be seen below, a number of functional studies has revealed activities of endorphins on immune cells that are not prevented by naloxone pretreatment, and/or do not need the N-terminal tyrosine present on all known endorphins, suggesting that endorphin-receptors on lymphocytes may include additional subtypes of a non-opiate variety. The presence of preproenkephalin mRNA has also been detected in murine macrophages.[47]

The first report of an effect of opioid peptides on immune cells in vitro showed enhanced T-cell rosette formation by morphine or ME.[99] These effects were blocked by naloxone, and were later extended to LE.[55] By contrast, a subsequent study found that βE (10^{-11} M) *suppressed* T cell rosetting, whereas ME and LE had no effect.[16] Enkephalins and βE have also been shown to enhance lymphocyte proliferative responses,[28,70] but whereas the responses were prevented by naloxone in one report,[70] they were

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