MECHANISMS OF PHYSICAL AND EMOTIONAL STRESS

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PSYCHOLOGICAL INFLUENCES ON IMMUNITY: MAKING SENSE OF THE
RELATIONSHIP BETWEEN STRESSFUL LIFE EVENTS AND HEALTH

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INTRODUCTION

During the last two decades there has been ample
documentation of the relationship between an accumulation of
negative major life events and subsequent health impairments.
Although there are a number of methodological problems with
many of these studies, the consistency and pervasiveness of
the effects are striking1,2. However, throughout most of
this literature the size of the relationship between the
number of negative life events and subsequent illness has
been modest, with most studies showing correlations in the
range of .304. In fact, most individuals who experience
major life events do not become ill, or they only experience
relatively short illness episodes that are frequently quite
comparable to those experienced by their population age-
mates.

In this chapter we will present a conceptual framework
for understanding the relationship between stressful events
and an increased risk for infectious disease. We argue that
an increase in psychological distress, sustained over time,
leads to adverse immunological changes; these distress-
related immunological changes provide one physiological
pathway through which major and minor life changes could lead
to an increased incidence of infectious disease and perhaps
malignant disease.

While many distressed individuals may show immunological
changes, actual organically-based illness episodes are a
function of differential exposure to pathogens, as well as
the prior health of the individual, particularly in regard to
immune system function. Across those individuals who have
equal exposure to an infectious agent, e.g., a virus, the
probability of developing a clinical illness is likely to be
at least partially dependent on the prior status of the
individual's immune system, as is the intensity and duration
of any clinical illness episode.
Extending this rationale, those individuals who are presumably most likely to show health changes in response to stressors are those whose immune system function is already compromised to some extent, either by an immunosuppressive disease like AIDS, or by a natural process like aging that is associated with immunological impairments. These individuals are more likely to be at risk because they are more likely to have poorer immunological defenses at the onset of a stressor; smaller stress-associated immunological decrements could have more important consequences. More speculatively, other at-risk groups could include chronically distressed individuals because of longer-term immunological changes.

While this conceptual framework is logical and consistent with considerable epidemiological data, a major caveat to be kept in mind is the paucity of certain kinds of critical supporting evidence. Very few studies have simultaneously shown a triad of heightened distress, impaired immune function, and actual health changes in the same individuals; most studies have simply shown that two of the components may co-exist, e.g., distress and immunological alterations.

We will discuss possible connections among the heightened distress generated by major or minor stressful events, alterations in immune function, and actual health changes; evidence for each of the linkages will be examined separately. We will first describe evidence linking changes in immune function with illness, followed by discussions of the evidence linking greater distress (a reliable by-product of stressful life changes) with both immunological alterations and health changes. Finally, we will discuss the few studies that have included all three components and have shown a confluence among distress, immunity, and health changes.

IMMUNITY AND HEALTH

There is excellent evidence that individuals with significant impairments in immune function are at greater risk for infectious disease, at least among individuals who have major immunological impairments. For example, individuals with immunosuppressive diseases like AIDS, or individuals on immunosuppressive therapies like chemotherapy are at great risk for death from opportunistic infections3.

Also relevant for our discussion is some of the work with older adults. Poorer immune function has been associated with higher rates of mortality in individuals over 80 years of age4. Pneumonia and influenza constitute the fourth leading cause of death among the elderly4. While the exact nature of immunological alterations associated with aging have been widely debated, there is good evidence that functional or qualitative aspects of immunity appear to be poorer in older adults6,7.

There is also evidence that persistent nutritional problems are associated with immunological impairments and poorer health8. Taken together, there is consistent evidence that individuals with moderate to severe impairments
in immune function are at greater risk for infectious
disease. The links between mild or transient immunological
impairments and health are not well-established.

IMMUNITY AND "STRESS"

Acute Stress

In a series of studies using medical student subjects,
we have compared immunological and psychological data
obtained during examinations with comparable data obtained
one month previously when students were not taking
examinations. Using this paradigm we have found differences
in NK cell lysis using two different target cells, as well as
differences in NK cell percentages using two different
methods. We have found poorer blastogenic
responsiveness with two mitogens, concanavalin A (Con A) and
phytohemagglutinin (PHA), lower percentages of total T-
lymphocytes, lower percentages of helper and suppressor T-
cells, lower percentages of total lymphocytes, and poorer
gamma interferon production in lymphocytes stimulated with
Con A.13

We also found higher antibody titers to three latent
herpesviruses, Epstein-Barr virus (EBV), herpes simplex virus
using a Type 1 antigen (HSV-1), and cytomegalovirus during
examinations.14 Higher titers during examinations with lower
levels during baseline periods are thought to reflect poorer
cellular immune system control of virus latency.15

Other investigators have found immunological changes
associated with relatively commonplace stressful events. For
example, Stone and colleagues16 collected mood ratings over
an eight-week period, with concurrent collection of parotid
saliva in an intensive study of a small cohort of dental
students. The antigen specific secretory immunoglobulin A
response to a harmless protein (rabbit albumin) was lower on
days with high negative mood relative to days with lower
negative mood; similarly, the secretory immunoglobulin A
response was relatively higher on days with high positive
mood, in contrast to days lower positive mood.

There is also evidence that bereavement and/or major
depressive disorder may have adverse immunological
consequences. Two studies of bereaved spouses have shown
poorer blastogenic responsiveness following bereavement. In
a cross-sectional study Bartrop and colleagues17 found
differences between bereaved spouses and nonbereaved
comparison subjects. In a prospective study Schleifer and
colleagues18 found poorer mitogen responsiveness after the
death of a wife than before bereavement among men whose wives
had terminal breast cancer. Major depression has also been
associated with poorer cellular immune function.19,20

Chronic Stress

There is some evidence that exposure to chronic physical
stressors (e.g., noise, shock, or rotation) may produce
immunological adaptation or even enhancement of immune
function in rodents.21,22 In contrast, acute stressors are
generally associated with immunological decrements.\(^{23}\)

Data from longitudinal studies of marital separation/divorce suggest that adaptation following separation occurs over a several-year period. Weiss\(^{24}\) suggests that the establishment of a more resilient and stable identity may take 2-4 years. Data from a longitudinal study showed that it was 3.3 years after separation before the average woman's life assumed a sense of coherence and stability.\(^{25}\) Cartwright\(^{26}\) found depression-related REM sleep alterations that persisted two years after divorce in a sample of women. We were interested in the possibility of similarly persistent distress-related alterations in immune function following separation.\(^{27}\) Self-report, immunological, and nutritional data were obtained from 38 separated or divorced women and 38 sociodemographically-matched married women. Women who had been separated one year or less had significantly poorer qualitative and quantitative immune function than their well-matched married counterparts. Moreover, among the separated/divorced women we found that shorter separation periods and greater continuing attachment to the (ex) husband were associated with poorer immune function and greater depression. Analyses of data from the married women showed that poorer marital quality was associated with both a poorer response on qualitative assays of immune function, as well as greater depression. These data are consistent with the epidemiological evidence that has linked marital disruption with increased mortality and morbidity, discussed shortly.

Other cross-sectional evidence also suggested that chronic stress was associated with more chronic immunological alterations. Immunological and psychological data obtained from 34 men and women were providing long-term care for a family member with Alzheimer's Disease.\(^{28}\) Caregivers had significantly lower percentages of total T-lymphocytes and helper T-lymphocytes than sociodemographically-matched comparison subjects, as well as significantly lower helper/suppressor cell ratios. Caregivers also had significantly higher antibody titers to EBV than comparison subjects, suggesting that cellular immunity was less competent in controlling virus latency in the former. There were not significant differences between the groups in the percentages of natural killer cells or suppressor T-lymphocytes. Caregivers were significantly more distressed than comparison subjects.

Thus, evidence from two more chronically stressed samples of human subjects that suggests that prolonged or chronic psychological stress in humans does not lead to adaptation to the level of well-matched comparison subjects, in contrast to data from rodent studies. Moreover, these data suggest that chronically distressed individuals could be at greater risk for infectious illness. Epidemiological data, discussed below, provide some indirect support for these assumptions.

**EPIDEMIOLOGICAL EVIDENCE: HEALTH AND DISTRESS**

There is a voluminous literature showing that higher
numbers of stressful life events are associated with both
greater distress and increased health risks\(^1\)\(^2\) that is too
to extensive to review here. Similarly, there are considerable
epidemiological data consistent with higher rates of
morbidity and mortality in more distressed populations. For
example, the mortality rate among psychiatric patients is one
and one-half to two times as high as among nonpatients, even
when such high-risk groups as the chronically ill, aged, and
alcoholic subpopulations are removed from consideration.\(^9\)
There is also evidence of greater cancer mortality among
psychiatric patients\(^3\)\(^6\), as well as among nonpsychiatric men
who may be more depressed.\(^3\)\(^1\).

There is also evidence of significantly higher mortality
among bereaved, separated, and divorced individuals.\(^3\)\(^2\)\(^3\)\(^7\). Separated
and divorced individuals are at much higher risk
for both mental and physical illness than are their married
age-mates.\(^3\)\(^4\). While much of the relevant epidemiological
literature does not provide data for infectious disease
separately from other causes of morbidity and mortality,
there is some evidence of significant risks for infectious
disease associated with marital disruption. For example,
separated/divorced adults have six times as many deaths from
pneumonia as married adults\(^3\)\(^7\). Separated women have 30
percent more acute illnesses and physician visits than
married women\(^3\)\(^5\).

As noted earlier, poorer immune function has been
associated with higher rates of mortality in individuals over
80 years of age\(^3\)\(^4\), and pneumonia and influenza constitute the
fourth leading cause of death among the elderly.\(^5\) However,
distress may have some important additive effects in this
population: within the first year after psychiatric
admission, there are fifty times more deaths from pneumonia
among elderly psychiatric patients than found among their
age-matched general population counterparts.\(^3\)\(^8\). The ratio
drops to twenty times that of their age-matched counterparts
by the second year of hospitalization, suggesting that the
hospital environment per se may not be as important a factor
as the transition.

Moreover, while it is reasonable to assume that psychia-
tric inpatients are more distressed than community residents
on the average, it should also be noted that depression is the
modal reason for psychiatric hospitalization in the elderly.\(^3\)\(^9\).

If psychological resources like social support moderate
distress and concurrently attenuate adverse immunological
changes, then individuals with less interpersonal support
should be at higher risk. A number of other investigators
have also found evidence of lower morbidity and mortality
associated with greater support.\(^4\)\(^0\)\(^-\)\(^4\)\(^2\).

CONVERGENT EVIDENCE: DISTRESS, IMMUNITY, AND HEALTH

There are few studies to date in which investigators
have simultaneously found heightened distress, poorer immune
function, and adverse health changes in the same individuals.
The relative scarcity of such essential evidence may be
related in large part to the low base rates for minor illness

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among relatively healthy populations; within a period of several months only a minority of individuals will actually fall ill. In addition, the accuracy or reliability of subjects' recall for short episodes of infectious disease is certainly better for more recent illnesses, so that differences in recall in studies demanding longer-term recall may obscure differences in illness rates as well.

Medical Students

We have not found significant differences in the health of our medical student subjects when we compared days of self-reported illness in baseline periods with illness during examinations, even though there were significant differences in immune function and distress. However, in these earlier studies from our laboratory we obtained health information only for relatively brief time periods. In more recent work we have been following first-year medical students longitudinally, across the course of the academic year, and we are beginning to find differences in self-reported health using this strategy. We obtained serial blood samples from 40 students during the first, third, and fifth examination periods, as well as one month before each. We found significant decrements in a variety of immunological measures during examinations as compared to baseline, including large changes in the production of gamma interferon by concanavalin-A stimulated lymphocytes, as well as changes in both plasma and intracellular levels of cyclic AMP. Moreover, changes in two different herpesvirus assays suggested reactivation of latent virus, and therefore poorer cellular immune system control of latent virus; antibody titers to EBV fluctuated markedly during examinations, while T-cell killing by memory T-lymphocytes of EBV transformed autologous B-lymphocytes simultaneously declined during examinations.

Consistent with these immunological changes, our medical student subjects reported an increase in infectious disease symptoms, particularly upper respiratory tract infections, in the two weeks preceding and the two weeks following examination periods, compared to the comparable time periods around the baseline or low-stress samples. As in our past research, students also reliably reported greater distress during examinations.

Disclosure of Traumas and Immunity in Undergraduates

Psychotherapy is associated with a reduction in distress and positive behavioral changes. In addition, there is some evidence that even brief psychotherapy or psychological consultation is associated with fewer outpatient medical visits, fewer days of hospitalization, and lower medical costs. Neither the mechanisms underlying these effects nor their generalizability is known.

In previous work from our laboratory we found that a distress-reducing intervention (relaxation training) was associated with improvements in some aspects of cellular immune function in older adults. These data suggested that the reduction of distress might be associated with positive immunological changes.
In a subsequent study, it was hypothesized that actively confronting upsetting experiences would have positive physiological consequences. Fifty healthy undergraduates were randomly assigned to write about either traumatic experiences or superficial topics for four consecutive days. Those subjects who wrote about traumatic events demonstrated an overall higher mitogen response following baseline in comparison to control subjects. Comparisons of the number of health center visits in the 15 weeks prior to the study with those during the six weeks of the study showed a significant drop in the number of visits for trauma subjects relative to those of controls. Although subjects in the trauma condition initially reported some negative feelings associated with the experiment, they were significantly happier than controls at the three-month follow-up. In addition, those participants who wrote about experiences that they had previously "actively held back" in discussions with others (n = 11) had a better proliferative response than those subjects who had not similarly held back (n = 14). Consistent with the results of our intervention study with older adults, these data suggest that psychotherapy or other distress-reducing therapies may have positive consequences for immune function and health.

**West Point Cadets**

In an innovative use of an opportunistic data set, Kasl and colleagues examined psychological and immunological data from cadets who were seronegative for EBV (not latently infected) on entry into the West Point. Data collected over the four years the cohort was followed showed that a distress-related triad of risk factors (higher levels of motivation for a military career, poorer academic performance, and having a father who was an "overachiever") was associated with three illness indices: an increased risk for seroconversion, longer hospitalization in the infirmary following seroconversion, and higher antibody titers to EBV among those who seroconverted in the absence of clinical symptoms.

These data are consistent with the alterations in cellular immunity noted in the medical students during examinations, particularly those related to herpesvirus latency. Taken together, these data also provide empirical support for the anecdotal speculation that has linked stress and the appearance, duration, and intensity of herpesvirus infections.

**Other Considerations**

There are a number of other factors that could contribute to poorer health in more distressed individuals. For example, Verbrugge suggests that formerly individuals might have poorer health than their married counterparts because they may engage in other more risky behaviors, e.g., they may smoke, drink, have poorer diets, or sleep more poorly. In research from our laboratory we routinely include two biochemical nutritional assays with relatively longer and
shorter half-lives; the data from these two plasma protein markers provide objective evidence of important aspects of nutritional status. We exclude data from subjects who are out of the normal range on these markers, or who report alcohol or drug abuse. While we find minor differences in sleep between more or less distressed subjects, they are not reliably correlated with immune function. Thus, although such factors may certainly play an important role in population differences in health, there is also evidence of physiological alterations in normal individuals that appear independent of these factors.

IMPLICATIONS

Reiterating our original proposal, we suggest that distress-related alterations in immune function may lead to greater health risks. We argued that behavioral influences on immunity were likely to have the most important health consequences for those individuals who were already vulnerable, either because their immune function is already compromised by a natural process like aging, or through more chronic stress-related alterations. While there may be some adaptation over time, prolonged or chronic psychological stress in humans does not appear to lead to adaptation to the level of well-matched comparison subjects. Epidemiological data indirectly support these assumptions, providing evidence of greater morbidity and mortality among more distressed populations. However, there are still very few studies to date in which investigators have simultaneously found heightened distress, poorer immune function, and adverse health changes in the same individuals; these data are essential for the demonstration of the relationship.

REFERENCES


