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88 Psychological Stress, Immunity, and Physical Disease

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I received my doctorate in social psychology in 1973 and began my career studying the effects of environmental stressors, such as aircraft and traffic noise, on children's cognition and behavior. In the 1980s, I became interested in the role of stress in physical health, particularly through its effects on the immune system. To pursue my new interest, I needed to expand my knowledge base. I convinced the National Institutes of Health to provide me with support to train in immunology, endocrinology, and virology. Questions I planned to address included: Does stress influence the immune system's ability to fight off infectious disease? What types of stressful events put people at risk for getting sick? How does stress influence the immune system to increase vulnerability to disease?

During the next few years, my laboratory and others found that experiencing stressful events (e.g., death of a loved one, taking an important exam); feeling stressed, anxious, or depressed; and performing stressful tasks in the laboratory all were associated with poorer functioning of the immune system. Immune measures used in these studies were primarily tests of the ability of immune cells drawn from participants' blood samples to respond to foreign (non-self) substances. It was unclear whether these stress-associated immune changes observed *in laboratory petri dishes* represented the type or magnitude of change necessary to influence the body's ability to fight infection.

psychological stress (experiencing stressful events) = death of a loved one, taking an important exam; feeling stressed/ anxious/depressed; performing stressful tasks in a laboratory setting; etc.

Does Stress Influence the Immune System's Ability to Resist Infectious Disease?

In 1985, I traveled to Great Britain to meet with Dr. David Tyrrell, a physician and virologist who headed the British Common Cold Unit (CCU) in Salisbury. The CCU was founded just after World War II with the mission of learning the causes of, and developing a cure for, the common cold.

I convinced David to collaborate on a study investigating whether stress plays a role in people's ability to resist infection and illness. Between 1986 and 1989, we collected data from more than 400 healthy

Hypothesis: Stress -?-> People's ability to resist infection & illness

Subject: 400+ healthy volunteers

Instruments: Questionnaires measuring # of major stressful life events, perceived stress (whether demands exceed ability to cope), & negative emotions

Lab condition/manipulation: participants exposed to 1 of 5 cold viruses thru nasal drops --> being observed at the CCU for 6 days --> see if they developed colds

volunteers, using questionnaires to measure the number of recent major stressful life events (e.g., death of spouse, job loss), perceived stress (perception that demands on them exceed their ability to cope), and negative emotions (e.g., anxiety, depression). Subsequently, through nasal drops, we exposed each volunteer to one of five viruses that cause a common cold, and then we followed them in quarantine at the CCU for six days to see if they developed colds. A cold was defined as both being infected (study virus replicates in the body and is found in nasal secretions) and showing symptoms of illness. Overall, about one-third of exposed participants developed a cold. We found that the more stress participants reported (on any of the stress measures), the greater the likelihood that they developed a cold when later exposed to a cold virus.

***Results: Just about 1/3 of the exposed participants developed a cold! 2/3 did not!!!

***More stress participants reported (on any of the stress measures) --> the more likely they developed a cold when exposed to a cold virus!!!

In this and subsequent studies, we measured stress *in healthy participants before they were exposed to a virus*. Consequently, we could rule out the possibility that either existing illness or developing a cold in our study caused participants to report more stress. Moreover, we were able to measure and eliminate (through statistical adjustment) other explanations for our findings, such as heightened stress and disease susceptibility both being caused by participant age, education, sex, weight, height, or pre-existing immunity (antibody level) to the experimental virus.

Budgetary constraints resulted in the CCU closing in 1990. Nevertheless, we were able to continue our work because one of the five remaining laboratories in the world that conducted viral exposure studies with human participants was located in Pittsburgh, where I lived and worked.

What Types of Stressful Events Put People at Risk for Getting Sick?

In the first Pittsburgh study, instead of stress questionnaires, we used a life-event *interview* that identified each individual's most stressful life event, the *type of event* (e.g., interpersonal, educational, financial), and *how long it lasted*. After the interview, we exposed each of 276 participants to one of two viruses that cause a cold, and then monitored them in quarantine. We found that the *longer* participants' most stressful event lasted, the greater their probability of getting sick following viral exposure. Moreover, the types of events that were most predictive of colds were *enduring interpersonal problems* and being *under- or unemployed*.

stressful events most predictive of colds = enduring interpersonal problems 持久的人際關係問題 and underemployed 就業不足 or unemployed 失業

Subjects: 276 volunteers

Method: Life-event interviews --> to identify each individual's most stressful life event, the TYPE OF EVENT (interpersonal, educational, financial, etc.), & HOW LONG IT LASTED

Laboratory/Condition: participants exposed to 1 of 2 cold viruses --> being monitored in quarantine

***The longer participants' most stressful event lasted --> the greater their likelihood of getting a cold after exposed to a cold virus!!!

Results: Stress --> Increase in the risk of disease <-- NOT measured/explained by elevated levels of "stress" hormones (epinephrine, norepinephrine, cortisol), poorer immune function (thru in vitro analysis), or poor health practices (smoking, excessive alcohol consumption, poor diets, low levels of physical activity, poor sleep)

How Does Stress Influence the Immune System to Increase Vulnerability to Disease?

In the Pittsburgh study, we also tested whether stress predicted increased risk of disease because of its possible associations with elevated levels of "stress" hormones (epinephrine, norepinephrine, cortisol), poorer immune function (measured by *in vitro* assays), or poor health practices such as smoking, excessive alcohol consumption, poor diets, low levels of physical activity, and poor sleep. Contrary to expectations, none of these (alone or together) explained why stress was associated with greater risk of developing a cold.

New insights about the function of the immune system provided another possibility to explore. Chemicals called pro-inflammatory cytokines are released by the immune system in response to infections. These chemicals elicit an inflammatory response, drawing immune cells to the infected area to help orchestrate the immune defense against the infectious agent.*** However, if the immune system produces *too much* of these inflammatory chemicals, the results can be toxic. In the case of infection with a common cold virus,*** producing too much pro-inflammatory cytokine triggers cold symptoms, such as nasal congestion and runny nose.

function of inflammation 炎症 (release of pro-inflammatory cytokines) = draws immune cells to infected area to help produce immune defense against the infectious agent

too much pro-inflammatory cytokines (促炎性的細胞因子) = triggers cold symptoms

***Results: High levels of Stress reported --> High levels of inflammatory chemicals measured --> experiencing more cold symptoms

In 1999, we published a study that established the role of inflammation in the link between stress and colds. We measured perceived stress by questionnaire and then exposed participants to a cold virus. Following viral exposure, we measured how much pro-inflammatory cytokine was produced in participants' nasal secretions. We found that participants reporting high levels of stress both produced high levels of these inflammatory chemicals and, in turn, experienced more symptoms.

function of cortisol (皮質醇) = redcues inflamation by shutting off the release of pro-inflammatory cytokines

These results raised a dilemma for us. Acute stress exposures in the laboratory and natural settings had been found to *increase* circulating levels of cortisol, a glucocorticoid hormone which *normally reduces inflammation* by turning-down the release of pro-inflammatory cytokines. Yet even though acute stress was associated with increased cortisol (and hence would presumably decrease cytokine release),****** we found that people who suffered from chronic stress produced more, not less, pro-inflammatory cytokine.****** In response to this apparent contradiction, we hypothesized that when people are exposed to major stressful events over a prolonged period, their bodies adapt to the initial increase in cortisol by reducing immune cell responsiveness to cortisol (a process called glucocorticoid resistance). As cells become less responsive, the body loses the ability to turn down the inflammatory response.

acute stress exposures = produce more cortisol (glucocorticoid 糖皮質激素 hormone) that normally reduces inflammation

Hypothesis: Prolonged experiencing major stressful events --> bodies adapting to initial increase in Cortisol (by reducing immune cell responsiveness to Cortisol) = GC Resistance --> bodies losing the ability to TURN DOWN the inflammatory response

chronic stress exposures = cause the body to develop glucocorticoid resistance 糖皮質激素抵抗性 (adaptation to the initial increase in cortisol by reducing immune cell responsiveness to cortisol)

We began testing this hypothesis by examining whether chronic stress in humans was associated with reduced responsiveness to cortisol.

--> Autoimmunity Disorders

Subjects: parents of children with cancer (a population that experiences an intense, chronic stressful event) -- control group (similar non-stressed parents of healthy children)

Method: took blood samples from parents, added a synthetic cortisol-like GC (Dexamethasone) --> in order to (test its ability to) reduce their immune cells' ability to produce inflammatory chemicals (an expected result)

In a paper published in 2002, we identified a population that was experiencing an intense and chronic stressful event – parents of children with cancer – and compared them to similar non-stressed parents of healthy children. As expected, when we added a synthetic cortisol-like glucocorticoid, dexamethasone, to blood samples from parents of healthy children, it reduced their immune cells' ability to produce inflammatory chemicals. However, adding dexamethasone to blood samples from parents of cancer patients was relatively ineffective in reducing the production of these chemicals. That is, immune cells in chronically stressed parents were insensitive to the regulatory effects of this cortisol-like glucocorticoid.

***Results: Control non-stressed parents (with healthy children) --> Dexamethason was effective in reducing production of infllammatory chemicals!!!

Stressed parents (with cancer children --> Dexmethasone was ineffective !!!

***Chronic Stress --> insensitivity to GC's regulatory effects

Finally, in two studies published in 2012, we tested the implications of stress-elicited insensitivity to cortisol for susceptibility to disease. We found that interpersonal stressful events lasting a month or longer were associated with a decrease in immune cells' sensitivity to cortisol. In turn, less sensitivity to cortisol was associated with both greater production of pro-inflammatory cytokines in response to being infected by a cold virus, and with a greater risk for developing a cold.

Hypothesis: Stressful events (which ones?) --> Body's insensitivity to Cortisal --> Susceptible to disease

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Interpersonal stressful events lasting a month or longer --> decrease in immune cell's sensitivity to Cortisol!!!

In sum, in over 30 years of research, we found that psychological stress increases the risk of developing a common cold for those exposed to a cold virus; that long-lasting stressors, interpersonal stressors, and unemployment are particularly potent; that the association between stress and disease occurs because chronic stress interferes with the body's ability to turn off the immune system's production of inflammatory chemicals; and that this failure in regulation (maintaining a proper level) of immune response occurs because chronic stress results in immune cells becoming insensitive to cortisol.

*****Psychological Stress --> increase the risk of developing a cold for those who have been EXPOSED to a cold virus

Potent stressors = LONG-LASTING (prolonged) stressors, INTERPERSONAL stressors, & UNEMPLOYMENT stressors

What Are the Implications of This Research?

This work provides a broad psychobiological model of how stress influences health. It supports work by our lab and others on the importance of interpersonal and socioeconomic stressors, and the potent and unique effects of chronic stressful events. It also highlights that effects of enduring stress on health may not be driven by stress suppressing immune function, as we believed in the 1980s, but instead by stress interfering with the ability to *turn off* immune response when it is no longer needed.

Our demonstration of a relationship between stress and susceptibility to infectious disease has played an influential role in the medical community's increasing acceptance of the importance of psychological stress in health. Moreover, the hypothesis that chronic stress effects occur because immune cells become resistant to cortisol regulation is central

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to current understanding of how chronic stress influences risk for and progression of a broad range of diseases (e.g., heart disease, autoimmune diseases, diabetes) where inflammation plays an important role.

***Chronic Stress --> insensitivity to Cortisol (inability to "turn off" the immune response --> continuous inflammation --> progressive diseases (Heart Disease, Autoimmune Dieases, Diabetes, etc.)

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