

STRESS AND SUSCEPTIBILITY TO THE COMMON COLD

Sheldon Cohen, Ph.D.

Introduction

Dr. Sheldon Cohen is a Professor in the Department of Psychology at Carnegie Mellon University and an expert in the field of PNI. His research has provided the medical community with scientific evidence for something that many people have suspected for a very long time - that you are probably more likely to get a cold when you are under stress. Many investigators have shown specific correlations between changes in immune system measures and stressful events. This is especially the case in laboratory research using experimental animals. Dr. Cohen's studies are designed to assess whether the changes in specific immune cell functioning are sufficient to increase one's susceptibility to an infectious agent. Furthermore, these studies were designed to determine if a prediction could be made based upon a person's psychological state as to how likely he or she would be to manifest symptoms of clinical illness following exposure to a virus. These studies are important because they go beyond the test tube to address highly relevant questions that affect all of us.

Psychological State and Infection

"Just from waiting around for that plain little band of gold, a person can develop a cold." These lyrics from the musical, *Gypsy and Dolls*, written in the 1950's and popular again today, demonstrate how ingrained in our culture is the idea that stress is associated with susceptibility to illness, and particularly to colds. Unfortunately, there has been very little research in this area and little concrete evidence that this is indeed the case. Our own work has focused not only on whether stress may put people at higher

risk for developing colds, but also on how that might occur. What is it that stress would do to people that would make them more susceptible?

We start with the premise that stress causes some change in the body that leads to greater susceptibility to infectious disease. Two issues then need to be addressed. The first issue is exposure. That is, one way stress could make you more likely to develop a cold is by increasing exposure to upper respiratory viruses. We know, for example, that stressed people often seek out social support. They have contact with more people and are therefore more likely to be exposed to a virus. In the work reviewed in this presentation, we eliminate exposure as a possible explanation for the relationship between stress and colds. The other issue is immunity. In some way stress influences the immune system in a manner that makes people more susceptible to developing a cold, given exposure to a virus. A discussion of the potential mechanisms whereby this might occur are reviewed elsewhere in this Proceedings.

As noted by other contributors to this volume, there is a tremendous literature that links stress with alterations in immune function - that is, that people under stress exhibit changes in their immunity. What is less clear is whether the changes we find in immune function among people under stress are relevant for susceptibility to infectious agents. Are those changes of the magnitude and the type that are important in predicting whether people will be more or less susceptible to infectious agents?

In our work we investigate whether people under stress are more likely to develop a cold following exposure to an upper respiratory virus. The study I will describe is a large trial with over 400 people. All subjects were healthy, between the ages of 18 and 55, and not pregnant. During the initial assessment, psychological measurements, including stress measurements, were performed. Additionally, the individual's health practices and immune system were assessed. We then exposed the subjects to an upper

respiratory virus. The dose used in the study would be expected to induce clinical illness in roughly one-third of the participants.

The question posed when designing the study was, can we predict from psychological states assessed at the onset of the study who is going to develop clinical illness? Clinical illness was defined as a combination of two things: infection and symptomatology. First, the subjects had to be infected with the virus. Infection was indicated either by our detecting the virus in nasal secretions or by a significant increase in specific antibody to that virus in serum collected three weeks after the trial. Second, to meet the criteria of having a cold in these trials, a person had to have the usual symptoms people exhibit when they develop a cold, such as a runny nose, coughs and sneezes.

Before volunteers arrive at the unit for the trial, we collect demographics and medical histories. On the first two or three days of the trial, we draw blood and collect nasal secretions. The physician does an initial rating on a standard protocol of symptoms of upper respiratory infections. We also perform a physical exam since everybody has to be in perfect health to go through the trial. Finally, we measure health behaviors, such as smoking and dietary practices, and psychological variables, including those indicative of stress.

After we collected those data, we inoculated the participants either with one of five upper respiratory viruses or with saline. Three of the viruses were rhinoviruses, one was a respiratory syncytial virus, and the other a coronavirus. With their heads tilted back, subjects received viral particles in each nostril. None of the people who were given saline developed colds.

On days four through eight, everyone was in isolation. We performed daily nasal washings so that we could look for the virus and determine if the person was infected. This is accomplished by placing saline into the patient's nostrils and letting it drop into a petri dish. We also had them place used tissues into a plastic bag

which we then counted and weighed. Each day of the trial, a physician assessed the severity of their symptoms taking precautions not to spread the infection. This individual was blind to the volunteers' psychological state and also blind to whether the volunteers received saline or virus. The assessment consisted of a standard upper respiratory symptom protocol.

At the end of the trial, both the physician and the patient used the same scale to determine whether a cold had occurred, and how severe that cold was. It turns out there was 94 percent agreement between the physician and the volunteers, confirming that people know when they have colds. Three weeks later, we collected the final blood sample to determine if there was a significant increase in specific antibody, one of our measures of infection.

Psychologists define stress as a situation in which demands exceed one's ability to cope. In this particular study, we used three measures of stress. One was a major stressful life event scale. The second a perceived stress scale. Perceived stress is the person's perception that the demands on them exceed their ability to cope at a particular time. The third scale was a negative mood scale, which documented a number of different negative moods, such as anxiety, depression and anger. These three scales are highly correlated so the data that is presented will be an index based upon the combined results of these three scales.

A number of different factors in this study were controlled for, including age, gender and education level, as well as serostatus - that is, whether the individual had antibodies to the virus that they're exposed to prior to exposure. Their allergic status, which virus they get, their body weight divided by their height, and the season of the year were also determined. Since data were collected over three years during different seasons, we were concerned about the possibility that 'stressed' people might be more likely to participate in the Winter or the Summer. Consequently, we controlled for this possibility as well. Thus, the data that are presented to address the question, "What is the relationship

between stress and infection susceptibility?" reflect controlling for the possible contributions of any of these factors.

Stress and the Common Cold

One of the most important observations stemming from this study is that there is a dose response relationship between the stress index and the probability of developing a cold. With every increment in stress, there was an increased probability of developing a cold. One of the things we were interested in was whether the effect occurred similarly for each of the viruses, or whether it occurred in just certain of the viruses used. Further analyses of the data revealed that the effect was similar across the five different viruses, even the corona and respiratory syncytial viruses, which are very different from the rhinoviruses.

These data reveal that stress increases susceptibility to a cold-causing virus, but they do not reveal the underlying mechanism for this phenomenon. A number of possibilities were considered. The first one was health practices. We know that people under stress smoke more, drink more, exercise less, don't sleep as well, and don't eat as well. Could it be that stressed people, because of their poor health practices, exhibit a greater susceptibility to viral infection? When we controlled for these health practices, it became apparent that they were not responsible for the observed link between stress and infection susceptibility. It should be noted, however, that smoking and alcohol consumption were both predictors of increased susceptibility, but they did not account for the relationship between stress and susceptibility to colds in this study.

The immune system was assessed in two ways. One was the measurement of total antibody and the other was a white blood cell count which also included an assessment of the number of lymphocytes, monocytes and neutrophils. While not as meaningful as other methods available for assessing the immune system, these were cost effective and appropriate since this was an initial study.

Total antibody levels were evaluated just prior to viral exposure. We wanted to determine if this measure might be correlated with stress and, if so, whether it would account for the relationship between stress and susceptibility to colds. We asked the same question with respect to white blood cell count. In both cases, if you take out the possible associations between these measures and cold susceptibility, stress still predicts susceptibility to cold virus. None of the immune measures did, nor did they account for the relation between stress and colds.

Conclusion

In conclusion, we know that stress puts people at higher risk for upper respiratory infections. What we don't know so far is why. We know it isn't due to changes in health practices, we know it isn't total immunoglobulins, and we know it isn't white blood cell count. Our current studies are designed to assess the contributions of a number of additional factors that might be indicative of potential mechanisms. For example, a variety of stress-related hormones, including epinephrine, norepinephrine, and cortisol, are being studied to determine if they play a role. We know that changes in these hormones can alter immune function, so we want to know if they are in part responsible for mediating the effects of stress upon cold virus susceptibility. In this next phase of the research, we are also going to assess the function of immune system cells rather than just perform quantitative measures as we did in the previous study described in this paper. In particular, we are focusing on natural killer cell activity, the ability of lymphocytes to produce interferon, as well as other measures that we think may be associated with the development of increased susceptibility to colds. Finally, we are continuing to look at possible behavioral mediators in addition to the health practices we've already examined, for example, how people cope with their stress. One of the things we are interested in is the possibility that more active coping with stressful events may alter hormonal and immune function and therefore serve as a primary mediator. So, in

future research we will carefully assess how people cope with each stressful event that they report.

DISCUSSION

Question: Would you comment about your observation that smoking and drinking were not factors during the course of your studies?

Dr. Cohen: In fact, of the health practices, both smoking and drinking relate to developing a cold. Smoking puts people at higher risk, and moderate drinking for people who don't smoke actually puts them at somewhat lower risk for developing a cold. But the question here is, can smoking and drinking explain the relationship between stress and a cold. For example, is it that stressed people smoke more and because they smoke they develop a cold? Even though smoking and drinking alcohol are related to susceptibility, neither explains the stress-susceptibility relationship. It is an independent effect.

Question: I was curious that no one in your control group developed colds. Did they know that this was a cold-related study?

Dr. Cohen: They all knew it was a cold-related study. However, only persons receiving viruses developed clinical colds. The saline group serves primarily to help keep investigators blind to whether or not any specific volunteer received a virus. As apparent from the results, neither volunteers nor investigators diagnosed colds in persons who were not infected.

Question: Can persons develop colds that are attributable to viruses other than the ones you exposed them to?

Dr. Cohen: Yes. Occasionally we get people with what we call 'wild colds'. They get colds that are not the one we gave them, and they get dropped from the study.

Question: You demonstrated a difference between illness in these two groups on the basis of their psychological rating. How about the incidence of infection? Was the infection similar in the groups independent of symptomatology?

Dr. Cohen: It becomes a little complicated, because it depends on how we look at stress. But in general, the stress index that I described is related to infection; it predicts infection. So if you split the notion of a clinical cold into two pieces, 1) are people infected, and if you only look at infected people, 2) do they develop a cold, the question then becomes does stress lead to the greater likelihood of infection, or does it lead to the development of symptoms among infected people? Each has different implications for mechanism. It turns out, at least using this particular index, that it actually predicts infection, but it does not predict the development of symptoms among infected people.

Question: Sorry, I didn't follow the last point. In other words, the occurrence of infection was the same?

Dr. Cohen: The answer is that stress does in fact increase the risk for developing an infection.

Question: The take-rate of the inoculum, if it were a vaccine, should also be affected by your stress factor. So if you had increased stress, the take-rate of a vaccine would be markedly affected by stress also?

Dr. Cohen: That's correct.

BEREAVEMENT AND THE THREAT OF MORTALITY INFLUENCE THE PROGRESSION OF HIV INFECTION

Margaret E. Kemeny, Ph.D.

Introduction

Dr. Margaret Kemeny conducts research that could very well help prolong the lives of many people who are suffering from AIDS. Dr. Kemeny is an Assistant Professor in the Department of Psychiatry at the University of California, Los Angeles. She is studying how emotional and psychological states may affect the progression of the AIDS virus. She has found that bereavement for a spouse or lover can accelerate immune system failure in HIV positive individuals. Her work also focuses on discovering interventions that could help AIDS patients cope with bereavement and other life stressors and potentially bolster the immune system.

The T-helper cell has been viewed as the conductor of the immune orchestra. Because of its ability to modulate so many other cells within the immune system, its ability to function properly is paramount if one is to successfully fight illness. Dr. Kemeny's studies are attempting to determine how psychological variables, especially the emotional changes that occur after losing a loved one, can influence the biological activity of this particular cell type. While not designed to demonstrate the mechanism whereby psychological variables can influence the immune system, these studies are, nonetheless, extremely important in that they show a relationship between how one reacts following stress and changes that can influence the progression of HIV.

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and
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