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Integrating Psychological and Immunological Variables

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Many behavioral scientists planning to conduct research on HIV infection and AIDS may be wondering whether to include immunological measurement in your project. Generally, I recommend that you do not.

What often happens is that an investigator has interesting questions that may involve immunological data in only a tangential way. That person writes a proposal that asks good, straightforward research questions, but then tags on immunological measures. When the immunological measures are not well integrated into the study, this part is often reviewed poorly. The strengths of the study may be ignored because there are so many problems in the immunological arm of the study.

The lesson, then, is that if immunology is not a central focus of your study, be cautious about including immunological measures in your proposal; there are many ways that data collection and interpretation can become complicated. After all, immunological measures are not an essential component of most HIV studies that examine psychosocial variables. If, however, you feel that immunological data is important to answer your research questions, then you should carefully consider the following issues.

Selecting an Immunologist as a Collaborator

The first critical decision is selecting the appropriate immunologist with whom to collaborate. Without an immunologist's help, you will not have the necessary experience to deal with the inevitable methodological issues or to interpret the data. Most behavioral scientists are usually not competent to interpret immunological data.

In selecting an immunologist to work with, you should be aware that immunologists specialize more than behavioral scientists do. They have particular cells or subpopulations that they study. This raises the question, "What immunological measures should you include?" That may be the choice of your immunologist, because he or she may already be running those assays in his or her lab. While some assays are routine,

many are complex, and it is not a simple matter to set up new assays. Thus, your immunologist may say that a measure you want to include is or is not possible within the available lab, timeframe, or budget.

Learning the Basics

Even if you are working with an immunologist, you should learn some basic immunology. For a psychologist or social scientist, it can be frustrating. Most medical school textbooks are unsatisfactory: "What is an antibody? Something that is stimulated by an antigen." "What is an antigen? Something that stimulates antibody production." Tautological explanations do not contribute to an understanding of the process.

If you want some basic immunology, which is a good idea for anyone working in the AIDS area, obtain an undergraduate microbiology text and read the two or three chapters on immunology. These books tend to be clearly written, and they will give you enough background so that you can read more advanced books, if necessary.

What to Measure

There are two general ways to assess immunological measures: (1) counting the number of immune cells and (2) evaluating how the cells function. In HIV infection, helper T-cell numbers are one of the markers of disease progression. With non–HIV-infected individuals, helper cells may change under stress, but it sometimes depends on the population, and so this is not a reliable measure.

Qualitative or functional aspects of immunity—how well cells function when exposed to a challenge or function—do appear to change with stress. For example, natural killer cell activity, an antiviral and antitumor defense, is one of the more reliable functions compromised by stress. Blastogenesis, which measures how lymphocytes proliferate when they are exposed to a substance called mitogen, is thought to provide a window for how lymphocytes proliferate when exposed to a pathogen, such as a virus or a bacteria.

When you choose your immunological assays, keep in mind that there are certain measures, noted in the psychoimmunological or immunological literature, that seem to change with stress and others that do not. These problems are compounded by HIV infection. With non–HIV-infected individuals, numbers of cells are not particularly stress responsive, while the functions of cells—natural killer cell activity, response to blastogenesis, lymphokine production—are more responsive to stressors.

Lymphokines, chemical mediators that stimulate immune function, tend to be depressed during stress. If you want to examine the relationship between stress and immune function, you may want to include both classes of assays if you have the resources. There is no single measure of immune function that gives you a measure of how the immune system is functioning, any more than there is a single measure of personality. The problem, then, is how to choose the measures to use in your study. For HIV, your single best measure is probably helper T-cells, but it would also be desirable to have other measures.

Cost

There is also the matter of cost. Immunological assays are expensive. If you look at hospital lab costs for helper T-cell assays, the costs of tests can range from $50 to more than $200 a test, depending on your

area of the country. At that price, an immunological measure should make a substantial contribution to your study.

Interpreting Data

In addition to how and what to measure there are also some considerations that may affect how your immunological data is interpreted.

Time of Blood Draw

You will need to draw blood from all individuals in a given study within the same two-hour period. There is diurnal variation in the immune system that may be related to compartmentalization. Thus, if you draw blood from some subjects at 10 a.m., some at noon, some at 2 p.m., and some at 4 p.m., those individuals may well have very different baseline immune function that relates solely to the time of day at which their blood was drawn.

There is also evidence showing that the amount of time blood sits before you conduct the assay makes a difference. So the lab will need to be able to conduct the assays in a timely fashion.

Age

When you are looking at an immunological assay for your particular population, you need to be aware of your particular sample. The age of your study population is an important consideration. After puberty, the immune system declines; those declines are most pronounced among older adults. For people over 75 years of age, for example, pneumonia and influenza are together the fourth-leading cause of death. By and large, younger people who are not HIV-infected do not usually die of pneumonia and influenza.

Drug History

Some of the immunological data suggest that if people have a history of intravenous drug use, even if they are now clean, their immune function at base line is often worse. If you have a sample that is mixed in terms of individuals with prior or current injection drug use and no prior use, you will have a population that differs substantially in immunological functioning at base line that may be unrelated to your research question.

Another confounding factor is alcohol and illegal drug use, which certainly has an adverse effect on immune function. If you have a population that is abusing drugs, you will certainly have impaired immune function. This is important data to gather, even though it is not clear how those effects may be mediated.

This confound can even extend to caffeine and cigarette use, since there is some data suggesting that both caffeine and cigarette use may alter immune function. Caffeine may only produce transient effects, like giving someone a shot of epinephrine. Cigarette smoking, both direct and passive, may both be related to lower immune function, so you want to know what proportion of your sample smokes.

Medication Use

You have selected your immunological assays, a nutritional assessment, a measure of health-related behaviors, and then encounter a major confound: medication use. In some ways, the best individuals to

study if we want to understand stress, health, and immune function are those who are going to be ill or who are already ill (i.e., HIV-infected individuals). However, HIV-infected individuals take a number of prescription and nonprescription medication, everything from megavitamin doses to AZT. Disentangling the effects of the medications from immune function when all of them may be immunoreactive is a major problem. The best way may be to have an adequate sample size so that you can control it statistically. You could use a control group of persons not taking any medication, but they would be more healthy than the experimental group and may differ in other ways that you could not control. For example, a larger percentage of older people take beta-blockers or estrogen. If you select only those who do not take medication, you are selecting survivors who may have abnormally active immune systems. In fact, one study that looked at unmedicated older individuals found that immune function appeared to increase with age, in contrast to the bulk of the immunological literature.

Health-Related Behaviors

One of the most important—and most often overlooked—problems will be the health-related behaviors that co-vary with stress (Kiecolt-Glaser & Glaser, 1988a). If a person is stressed, depressed, or upset in some way, they do things differently than people who are not. They are likely to eat more poorly, for example, and poor nutrition has adverse effects on immune function. Assessing nutritional status, however, is not an easy matter, and you will often end up doing quick measures (e.g., recent weight loss, normal range for height and weight, and perhaps plasma protein markers) that are not perfect, but are certainly better than nothing. With individuals who are already HIV-infected, there are concurrent nutritional changes that may also be taking place. These may be related to the infection, so it is important to be aware of what is happening in terms of nutrition.

Infection Illness

If you are assessing physical health and immune function, you want to know something about infectious illness in your subjects. This is one of the most difficult things to measure well because most physical health assessments look for global types of symptoms (e.g., malaise, fatigue, stomach aches). Those measures do not specifically relate to infectious illness. One of the batteries for measuring infectious illness is a health review that was developed for a study of air traffic controllers (Rose *et al.*, 1982a, b, c).

Final Thoughts

The key question is whether a relationship between psychological variables, actual changes in immune function, and illness exists. We now have good evidence for this relationship, albeit preliminary (Cohen *et al.*, 1991; Glaser *et al.*, 1992; Kiecolt-Glaser *et al.*, 1991).

The fact that stress can have adverse effects on immune function has been shown in a number of studies in both humans and other animals. If immune function is poor, a person's susceptibility to illness is much greater, especially with HIV. Anytime the immune system is suppressed radically, illness is more prolonged and more serious.

However, there is a paucity of data demonstrating the confluence of all three of those factors in the same individuals at the same time. That is important, because in most studies it is not possible to control whether someone becomes infected or not, nor can the dose of the pathogen be controlled. Therefore with semi-random patterns of infection, it is much harder to establish what is going on.

If you are not dissuaded, and you still want to include immunological measures in your behavioral study; that is good, because some of the stress/immune function data are among the most exciting. They have the potential to inform us about how stress, personal relationships, and health may be interrelated, and your well-designed study may make an important contribution (Kiecolt-Glaser & Glaser, 1988b).

References

Cohen, S., Tyrrell, D. A., & Smith, A. P. 1991. Psychological stress in humans and susceptibility to the common cold. *New England Journal of Medicine 325:* 606–612.

Glaser, R., Kiecolt-Glaser, J. K., Bonneau, R., Malarkey, W., & Hughes, J. 1992. Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. *Psychosomatic Medicine 54:* 22–29.

Kiecolt-Glaser, J. K., & Glaser, R. 1988a. Methodological issues in behavioral immunology research with humans. *Brain, Behavior, and Immunity 2:* 67–78.

Kiecolt-Glaser, J. K., & Glaser, R. 1988b. Psychological influences on immunity: Implications for AIDS. *American Psychologist 43:* 892–898.

Kiecolt-Glaser, J. K., Dura, J. R., Speicher, C. E., Trask, O. J., & Glaser, R. 1991. Spousal caregivers of dementia victims: Longitudinal changes in immunity and health. *Psychosomatic Medicine 53:* 345–362.

Rose, R. M., Jenkins, C. D., Hurst, M., Livingston, L., & Hall, R. P. 1982a. Endocrine activity in air traffic controllers at work: I. Characterization of cortisol and growth hormone levels during the day. *Psychoneuroendocrinology 7.* 101–111.

Rose, R. M., Jenkins, C. D., Hurst, M., Herd, J. A., & Hall, R. P. 1982b. Endocrine activity in air traffic controllers at work: II. Biological, psychological and work correlates. *Psychoneuroendocrinology 7:* 113–123.

Rose, R. M., Jenkins, D. C., Hurst, M., Kreger, B. E., Barrett, J., & Hall, R. P. 1982c. Endocrine activity in air traffic controllers at work: III. Relationship to physical and psychiatric morbidity. *Psychoneuroendocrinology 7:* 125–134.