Reading
Tracking the Source of Disease:
Koch's Postulates, Causality, and Contemporary Epidemiology

Criteria for determining cause-effect relationships in the study of disease
(Adapted from *Epidemiology in Medicine* by Hennekens and Buring, 1987.)

The following five criteria are used to help scientists determine whether there is a cause-effect relationship between a specific pathogen and disease. In general, more than one criteria must be met to support a hypothesis that a specific pathogen is the cause of the disease. The more criteria that are met, the stronger the evidence for a cause-effect relationship.

1. Strength of Association
Strength of association describes the strength of the relationship between exposure to the proposed pathogen and symptoms of the disease? If 99% of people diagnosed with a disease test positive for exposure to a particular pathogen, there is a stronger association than if only 65% of people diagnosed with the disease test positive for exposure to the pathogen. In general, a stronger association lends greater support for a hypothesis that the pathogen is the cause of a particular disease.

2. Biologic Credibility
Biologic credibility describes whether or not there is a logical proposed, possible mechanism for the cause-effect relationship. This proposed mechanism should be consistent with the current understanding of biology. For example, for a long time many people rejected the hypothesis that prions, which are proteins, were the cause of "mad cow disease". Many scientists rejected the hypothesis because there was no known explanation for how proteins could copy themselves and spread an infection to a new individual. Scientists have now proposed the hypothesis that prions change the shape of normal proteins and this is how they copy themselves in newly infected victims. While this mechanism has yet to be strongly supported by evidence, it does propose a biologically plausible mechanism.

3. Consistency with Other Investigations
This criterion refers to a pattern of similar results found by different investigators at different times, under different conditions, in different populations. For example, if a scientist in Zimbabwe finds a strong relationship between Bacteria X and Disease Y among male high school athletes, and a scientist in Australia finds the same relationship between Bacteria X and Disease Y among post-menopausal female business executives, then the relationship between Bacteria X and Disease Y is consistent among investigations. In general, the greater the consistency, the stronger the support for a

cause-effect hypothesis. Imagine a case in which scientists suspect that a disease common among both injection drug users and people with multiple sex partners is caused by a virus that can be transmitted by exchange of body fluids. Scientist A does a study on injection drug users and finds that all of them with the disease also have antibodies to the virus. Scientist B, however, does a similar study on people with multiple sex partners and finds that only 60% of those with the disease have antibodies to the virus. These results are not consistent and do not support the hypothesis that the virus is the cause of the disease.

4. Time Sequence

In order for a hypothesized cause-effect relationship to be supported, the exposure to the proposed pathogen must occur *before* development of the disease. For example, if an autoimmune disease causing brain degeneration were hypothesized to be caused by exposure to a common bacterium, then scientists would have to show that exposure to the bacterium occurred before onset of brain degeneration in order to support their hypothesis.

5. Dose-Response Relationship

Dose-response relationship describes a relationship in which greater exposure to the pathogen results in greater risk of contracting the disease. For example, consider a case in which people who are exposed to a protist in their water supply are coming down with severe diarrhea. Scientists test the water in homes and find that homes with the largest concentration of the protist in the water are also the homes with the greatest number of sick people. Homes with the smallest concentration of the protist in the water have the least number of sick people. Homes with intermediate concentrations of the protist in the water have intermediate numbers of sick people. The greater the concentration of the protist in the water, the more likely are people in the home to get sick. Another example of a dose-response relationship is the relationship between duration of exposure to tuberculosis and the likelihood of contracting the disease. People who live with family members that have active tuberculosis infections spend a lot of time indoors breathing air that contains tuberculosis bacteria on tiny droplets. A person who rides the same bus once a week with someone infected with tuberculosis is exposed to air containing the bacteria for a much shorter time. The person who spends more time indoors breathing air contaminated with the bacteria is more likely to develop tuberculosis. In general, a dose-response relationship between a pathogen and a disease supports the hypothesis that the pathogen is the cause of the disease.