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HOW TO TEST EVOLUTIONARY HYPOTHESES ABOUT DISEASE

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Testing an evolutionary hypothesis about disease is challenging. Even well-educated smart scientists make elementary mistakes in both directions. Many apparently plausible proposals turn out, on careful examination, to be preposterous. Conversely, many sensible proposals are incorrectly rejected because they are unclearly formulated, evidence is poorly marshaled, or because readers do not know how to assess evolutionary hypotheses. No cookbook guidelines can substitute for applying scientific method to a specific problem, and some hypotheses about the origins of vulnerability to a disease prove resistant to any straightforward test. Nonetheless, the below guidelines are offered to help structure clear thinking about how to formulate and test an evolutionary hypothesis about a disease. They are based on previous publications (Nesse, 1999; Nesse & Williams, 1995; Nesse & Williams, 1999), but have continued to evolve and will be improved further by thoughtful comments from readers. If you use these guidelines, please cite:
Nesse, Randolph M: *How to test evolutionary hypotheses about disease*, 2005, www.darwinianmedicine.org.

1. **Define the object of explanation with great specificity.**
    a. The object of explanation should be a trait shaped by natural selection (or a trait that for some reason cannot be shaped further by selection)
    b. A disease is an appropriate object of explanation only if the hypothesis is that the disease is not a disease at all but a useful defense.
    c. In most cases, the object of explanation is a universal trait that makes an organism vulnerable to a disease, relative to alternative possible designs.
    d. If the object of explanation is not a trait universal in the species, specify the special circumstances that justify this
        i. The most common exceptions are traits that reflect genetic differences characteristic of a subpopulation that increase ability to cope with localized challenges, such as sickle cell protection against malaria.
        ii. Other exceptions are facultative adaptations that are postulated to explain individual differences, such as the

system that adjusts the number of sweat glands as a function of early exposure to high temperatures. In most such cases the object of explanation is actually not differences, but the universal system that was shaped by selection to adapt individuals to particular environments.

iii. If the trait is a behavior, describe the behavior regulation system that gives rise to the behavior and how natural selection shaped it.

e. There is no evolutionary explanation for why one individual gets a disease and another does not. Evolutionary explanations are inherently about populations.

f. Evolutionary explanations are not alternatives to proximate explanations for how a mechanism works and why it goes awry in some people. Such proximate explanations are also needed, but they are not a substitute for an evolutionary explanation for why the body is the way it is. Evidence about proximate mechanisms is often very useful in assessing a hypothesis, however, especially when the hypothesis is that vulnerability to disease results from constraints or tradeoffs.

2. Specify all possible alternative hypotheses for what forces shaped the trait and why it is apparently suboptimal. There are six main possibilities.

a. The environment has changed faster than selection can keep up and the disease results from this mismatch.

b. The relevant environmental factor is another organism that evolves faster than selection can shape protective mechanisms

c. Constraints such as limited ability to clear mutations or path dependence make it difficult for selection to improve the design.

d. The trait offers benefits that account for its apparently suboptimal design.

e. The trait offers benefits to reproduction or to kin that explain the health costs to the individual.

f. The trait is not a disease at all, but a useful protective response.

3. Make explicit predictions from each possible hypothesis.

a. If the comparative method can be applied, use it. Nothing else compares in power. Admittedly, many hypotheses about disease are not susceptible to any direct comparative test, so weaker methods must be used.

b. Strong predictions are about previously unobserved aspects of the trait.

c. Additional predictions may be about the utility of the trait in different circumstances as compared to organisms that lack the trait either by genetic defect, genetic knockout, or pharmacological or other manipulation.

4. **Use all available evidence to test the predictions from all alternative hypotheses to arrive at a judgment about the contributions of different factors.**

    a. Note that multiple factors often operate together to explain an apparently suboptimal trait. This is quite different from a proximate explanation in which evidence for one alternative is usually against another.

    b. Nonetheless, many hypotheses can be falsified by evidence that a trait does not actually fulfill the proposed function, or that some other strong prediction is falsified.

    c. Often judgment is required to assess the overall plausibility of the proposal, always as compared to alternative hypotheses.

Some Common Mistakes

The above guidelines tacitly describe a variety of possible errors, some of which are made explicit below.

1. Attempting to explain a disease. (Instead, reformulate the question as an explanation for vulnerability to a disease)
2. Proposing an explanation based on what is good for the species. (This is group selection, an elementary error. Almost all evolutionary explanations must be based on advantages to genes or individuals)
3. Proposing adaptive functions for rare genetic conditions. (There are sometimes evolutionary reasons why deleterious mutations stay in the gene pool, but the explanation is hardly ever some useful function of the disease itself.)
4. Confusing proximate and evolutionary explanations (This is a common serious mistake. Knowledge about how the body works can be very useful in assessing an evolutionary hypothesis, but it is not a substitute for an evolutionary explanation.)
5. Thinking that evidence for learning influencing a trait indicates that no evolutionary explanation is needed. Learning is a capacity shaped by natural selection, and the pathologies that arise from learning mechanisms are likely to harm fitness.

6. Thinking that evidence for cultural differences in a trait is evidence against evolutionary influences. The behavioral mechanisms that give rise to culture were shaped by natural selection, and human behavior is strongly influenced by culture. An evolutionary approach to behavior does not imply that behavior is somehow "determined by the genes," only that the mechanisms that give rise to behavior and culture were shaped by natural selection. These mechanisms obviously are capable of profound flexibility, with attendant major benefits and costs.
7. Failing to consider all of the alternative hypotheses. (This is very common and very serious. All too often an author will propose one possibility without making the alternatives explicit)
8. Wrongly assuming that evidence for one hypothesis is evidence against another. (Multiple factors may all contribute to a complete explanation. Worse, they are likely to interact in complex ways. A correct explanation often incorporates multiple explanatory factors.)
9. Presenting all the evidence in favor of a pet hypothesis and all of the evidence against other hypotheses, instead of offering a balanced consideration of all evidence for and against all hypotheses. (This is rhetoric, not science. It is all too common, for good reasons arising from human nature, not just in testing evolutionary hypotheses but across the range of sciences. Nonetheless, such advocacy should be avoided if at all possible.)

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