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PERSPECTIVES

EVOLUTION AND IMMUNOLOGY:

The Economics of Immunity

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Immunologists have a firm grasp of the diversity of immune responses mounted by animals against bacteria, viruses, and parasites. Although Darwinian natural selection has been invoked to explain other types of biological diversity, it is still not clear how natural selection might shape patterns of immunoresponsiveness--what type of immune response to mount, and at what strength. This question, which is quite distinct from historical accounts of the origin of different types of immunity (1), is now addressed by the reports of Moret and Schmid-Hempel (2) and Nunn *et al.* (3) on pages 1166 and 1168 of this issue.

Adaptationist thinking--in essence, cost-benefit analyses with evolutionary fitness as the currency--has had a substantial impact in many areas of biology (4). It is central to understanding defense against predators in animals and defense against both pathogens and herbivores in plants (5). Such thinking also forms a natural framework for understanding the evolution of the immune system (6). Indeed, discussions of immunity are often couched in terms of the costs (resources used and tissue damage associated with an immune response) and benefits (killing of the pathogen). Progressing from such informal notions to testable hypotheses requires some way to measure the fitness costs of operating an immune system. In addition, ecological correlates of variations in immune investment, such as the degree of exposure to pathogen assault, need to be identified.

Evidence that immunity does not come cheap is based largely on the assumption that the substantial physiological perturbations associated with mounting an immune response will have an impact on the fitness of the organism (7). Direct evidence for fitness costs comes from the invertebrate immune system. Invertebrates possess an innate immune system whose cells

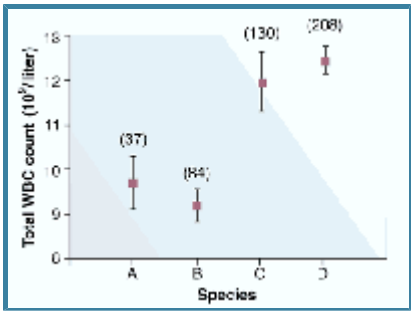
destroy pathogens by releasing soluble molecules or by engulfing (phagocytosing) them. In taxa as diverse as snails, moths, mosquitoes, and fruit flies, artificial selection in the laboratory for increased ability to resist parasite attack has been associated with reductions in at least some components of fitness (8). Moret and Schmid-Hempel (2) now report substantial fitness costs associated with activating an innate immune response in bumblebees. They found that immunologically challenging bees by exposing them to lipopolysaccharides or microlatex beads elicited antibacterial activity in the bee hemolymph ("blood") and also dramatically reduced their survival compared to bees that were not immunologically challenged.

There may also be fitness costs associated with immune responses in vertebrates. In addition to innate immunity, vertebrates possess an adaptive immune system in which different types of cells carry a highly diverse array of receptors that recognize an almost unlimited range of foreign antigens. One example of the fitness costs associated with mounting an adaptive immune response comes from immunizing wild birds with a human diphtheria-tetanus vaccine. Immunized birds fledged fewer and lighter offspring than nonimmunized birds (9). The mechanistic basis of these reductions in fitness remains to be determined for both the birds and the bees. In both sets of experiments, the animals were stressed: The bees were starved and the birds were producing offspring. When an animal is already stressed, mounting an immune response may place excessive demands on stores of an essential factor (a rare amino acid, energy?). Alternatively, stressed animals may be less able to repair damage that might occur as an incidental side effect of the immune response.

If immunity proves to be costly, natural selection ought to favor enhanced resistance to pathogens or immunoresponsiveness only when it is beneficial. Is investment in immune protection greater in species that are exposed to a larger number of pathogens? If so, this could explain natural variations in pathogen resistance or immunoresponsiveness. Analogous arguments underpin adaptive explanations of diversity in a wide range of animal traits. For instance, there is variation among mammalian species in regions of their bodies that have pronounced skin thickening. These regions correlate closely with those areas that are most likely to be severely damaged when males fight each other: Mountain goats use their horns to strike at the haunches of their opponents and have rump shields of thickened skin; in contrast, sheep, which meet squarely head to head, have thickened skin on the face and back of the neck (10). Is it possible to detect such ecological correlates of variation in the immune defenses of animals?

Nunn *et al.* (3) claim to have done just that in 41 species of primates. They gathered baseline white blood cell counts for captive female primates from zoo veterinarians (who considered these values typical for healthy animals). They discovered that total white blood cell counts, as well as numbers of the different types of white cells (neutrophils, lymphocytes, and monocytes), are higher in promiscuous primate species than in closely related monogamous species (see the figure). Nunn and co-workers argue that these results are evidence for greater investment in immune defenses by primate species more at risk of sexually transmitted diseases (STDs). They found no evidence that higher white blood cell counts were associated with greater exposure to ordinary infectious diseases because the counts did not correlate with body size or population density, or with exposure to soil-borne pathogens. Implicit

in Nunn *et al.*'s argument is that monogamous species find it too costly to maintain the slightly higher white blood cell counts typical of their promiscuous relatives.



Prime time for primates? Baseline white blood cell counts (mean ± SEM) for monogamous primates (**A**) the Bolivian gray titi (*Callicebus donacophilus*) and (**B**) the white-handed gibbon (*Hylobates lar*) and for their promiscuous relatives (**C**) the chimpanzee (*Pan troglodytes*) and (**D**) the yellow baboon (*Papio cynocephalus*). Numbers in parentheses refer to the number of blood samples contributing to the estimates. [Data from (3)]

The authors' assertion that species differences in white blood cell numbers recorded in zoos reflect evolutionary differences in immune defense investment provokes some difficult questions. Most important, are baseline white blood cell counts reliable measures of species differences in immune system preparedness? One argument might be that higher steady-state numbers of phagocytic cells such as neutrophils would enable these cells to reach points of infection in tissues more quickly. But the species differences in white blood cell numbers--which are often small compared to the health-related fluctuations observed in single individuals--will be rapidly swamped by the influx of bone marrow neutrophils into the blood in response to infection.

Even more difficult to explain are the higher numbers of lymphocytes in the promiscuous primates. It is the diversity of these antigen-specific cells and their capacity to make an effective memory response, rather than their overall numbers per se, that will determine the effectiveness of the immune response and the outcome of infection. Indeed, why are the numbers of all three types of immune cell (neutrophils, lymphocytes, and monocytes)--which have very different functions, life-spans, and evolutionary histories--elevated in promiscuous primate species? Perhaps the elevation of all three cell types reflects some other difference between promiscuous and monogamous primates. For example, in zoos, the housing arrangements (density of animals, and ratio of females to males) for promiscuous and monogamous species may differ. This could lead to varying degrees of exposure to stress and disease that may account for the differences in white blood cell counts. Even in nature, there might be species differences in circulating levels of stress or sex hormones resulting in differences in the numbers of white blood cells or their distribution within the blood, bone marrow, and tissues.

What of Nunn *et al.*'s argument that their findings point to a role for selection

imposed by STDs? Certainly these diseases are very widespread in nature and, although they typically have longer asymptomatic periods than other infectious diseases and cause chronic rather than acute infections, they can nonetheless cause substantial reductions in fitness--principally through sterility (11). Implicit in Nunn *et al.*'s argument (3) is the assumption that this selection pressure is strong enough to favor increases in costly immune machinery, but not strong enough to select for monogamy. That may be so, but we still have trouble imagining how slightly higher baseline numbers of white blood cells (principally neutrophils) could improve control of STDs. Neutrophils are primarily the frontline defense cells of the immune system, but it is the adaptive immune response of lymphocytes that controls chronic infection. If higher numbers of circulating neutrophils strengthen first-line defense in the urogenital tract, then why would they not do so in the respiratory and gastrointestinal tracts, sites of non-STD infection?

As is true for much comparative biology, the correlations reported by Nunn *et al.* are relatively weak. We will be delighted if their findings turn out to be an example of successful extraction of evolutionary signal from biological noise--indeed, many of the difficulties we have discussed would obscure rather than artifactually produce the correlation they report. Certainly, the idea that immune response variations in nature can be understood in terms of fitness costs and benefits is intuitively appealing (6). The principal challenge is to marry this idea with our detailed understanding of how immunity works. This may be difficult given the complexity and redundancy of the vertebrate immune system. Putative measures of immune investment must capture evolutionary differences rather than individual responses to current infections. For this reason, the interpretation of many measures of immunity in wild animals is difficult (12). Comparative studies with other measures of immunity--for example, the life-span of the thymus (an organ where T cells mature), the diversity of major histocompatibility complex antigens and their receptors, or genomic investment in immune-related genes--may become possible in the future.

Irrespective of the specifics of Nunn *et al.*'s argument, the species differences in baseline immune cell numbers highlighted by their study demand explanation. Extension of their analyses to other orders of mammals could be telling. Hopefully, attempts to test Nunn *et al.*'s interpretation will investigate fitness trade-offs between immunity and other competing demands on an animal (13). Used carefully, cost-benefit analyses should help to make sense of variations in immunity (6, 7)--not only variations between species, but also those associated with pregnancy, age, sex, and season of the year. They should also help to explain (and even to predict) which immune responses are used when and at what strength--behavioral versus physiological, adaptive versus innate, T helper cell type 1 versus type 2, and the amount of antigen required to elicit a response.

A cost-benefit approach to immunity might also be of substantial applied interest. Enhancing resistance to infection above that found in nature is the aim of certain selective breeding programs for domestic animals, and of attempts to genetically engineer mosquitoes to be more resistant to the malaria parasites that they transmit. Indeed, it is also the goal of much vaccination research. But, if the fitness costs of immunity prove to be substantial and widespread, then successful implementation of these resistance-enhancing strategies in the face of natural selection may prove harder than the technological challenge of creating them in the first place.

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