disease is manifest in these animals (*5*). Crossing mice lacking follicular dendritic cells or germinal centers (or those lacking chemokine/chemokine receptor combinations) with the autoimmune-prone MRL.Fas^{lpr} mice should help to elucidate the relative contributions of autoantigens, chemokines, and their receptors, and anti-apopotic versus proapoptotic signals in the generation of autoreactive B lymphocytes.

The study by William *et al.* (*5*) opens a new vista upon autoimmunity. Their work demonstrates that somatic hypermutation of autoimmune antibodies occurs outside of germinal centers in the autoimmunity-prone MRL.Fas^{lpr} mice. In the absence of the germinal center "checking" mechanism, there is rapid accumulation of high-affinity autoreactive B cells in the T cell zone of lymphoid tissues. The challenge now is to determine how migration to B cell follicles and the formation of germinal centers is prevented in the MRL.Fas^{lpr} mice and whether this is a general phenomenon that will be applicable to other autoantibodies and autoantigens.

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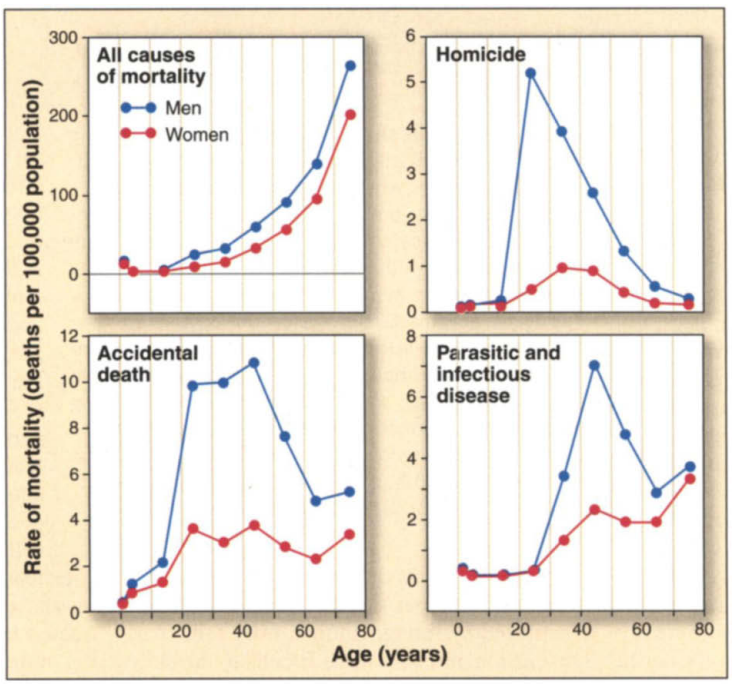
PERSPECTIVES: ECOLOGY AND EVOLUTION

Sex Differences in Mortality Rate

Ian P. F. Owens

Why do men typically die earlier than women in Westernized societies? The traditional explanation has been that men undertake more risky behaviors. Supporting this risk-prone behavior hypothesis are human demographic data showing that men are consistently more likely to die as a result of motor vehicle accidents, homicide, suicide, or accidents caused by firearms (*1*). Although the death rate through homicide in the United States is more than 10 times that in the United Kingdom and Japan, males are still twice as likely as women to be murdered in all three countries (*1*). The way in which the mortality rate changes with age also supports the risk-prone behavior hypothesis: The rise in accidental and violent death among men coincides precisely with the onset of puberty (see the first figure). On page 2015 of this issue, Moore and Wilson (*2*) propose that male-biased mortality may be caused in part by a greater susceptibility of males to infection by parasites, which in turn may be the result of male-male competition to secure mates and territory.



Sex differences in human mortality. The overall mortality rate in males is higher than that in females from puberty onward (**top left**). The other three graphs show sex differences in mortality rate due to homicide, accidental death, and parasitic and infectious diseases. For all three causes, mortality rate is higher in men than in women, but the timing of the onset of male-biased mortality varies across causes. For death through homicide and accidental causes (**top right, bottom left**), the increase in male-biased mortality begins immediately after puberty. For death caused by parasitic and infectious diseases (**bottom right**), the sex difference in mortality rate becomes apparent much later. [Data for 1997 USA population from (*1*) (www.who.int/whois)]

Traditionally, male-biased mortality among nonhuman mammals has also been explained in terms of more risky behaviors by males compared with females. Empirical studies of species in which males fight one another for access to females have shown repeatedly that such male-male competition can prove costly in terms of survival. Likewise, comparative studies demonstrate that the species with the greatest male bias in mortality tend to be those species in which male-male competition is the fiercest (*3*).

Moore and Wilson (*2*) now demonstrate that risky behavior by males is not the full explanation for male-biased mortality among mammalian species. They show that sex differences in mortality correlate with differences in susceptibility to parasitism between males and females. In those species where males die younger than females, the males suffer a disproportionately high rate of parasitism. The authors also show that male-biased parasitism is the general rule among mammals, and that it is most extreme in those species where male-male competition for mates is most severe. Taken together, these findings suggest that male-biased mortality occurs not only as a result of death through risky behavior, but also because males are more susceptible to parasitic diseases.

Human demographic data support the idea that parasites are an important determinant of male-biased mortality. Although sex differences in suicide and homicide grab the headlines, males are also more prone to a range of parasitic and infectious diseases (*1*). In the United States, United Kingdom, and Japan, men are approximately twice as vulnerable as women to parasite-induced death. In Kazakhstan and Azerbaijan, where the overall incidence of parasite-induced death is much higher, men

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Fight hard, die young. Male-biased mortality is well established in mammalian species. Male savannah baboons have a much higher mortality rate than females and also are much more susceptible to parasitic diseases. The susceptibility of males to parasitism may reflect their greater size or male-male competition for mates and territory (*10*).

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are more than four times as vulnerable to parasite-induced death. Furthermore, the increase in male-biased mortality is not simply associated with puberty, but typically occurs later in life (see the second figure). Together with Moore and Wilson's study of nonhuman mammals, these data suggest that differences between males and females in "immunocompetence"—an organism's all-round ability to avoid the harmful effects of parasites—may underlie the increase in male-biased mortality.

The classic explanation for low immunocompetence in male mammals is that masculinization depends on testosterone, an immunosuppressant (*4*). Long-term comparisons between castrated and "intact" men show that the former outlive the latter by up to 15 years. The life-prolonging effects of castration are proportional to the age at which the operation was performed (*5*). Moreover, because these comparisons have typically been based on institutionalized populations, the elevated rate of mortality among intact males is usually due to infectious diseases rather than violence or accidents.

The exact mechanisms by which testosterone causes immunosuppression are still under investigation. One possibility is that testosterone alters the way in which males allocate resources among competing needs. Males may be unable to mount an effective immune response because they face a trade-off between allocating resources to fending off disease and allocating resources to other activities. The most obvious resource is energy itself and, given the huge number of cells involved in immune defense, it is plausible that a prolonged response would be energetically costly. However, there could be trade-offs with respect to other scarce nutrients, such as carotenoids, which are important not only in many basic metabolic pathways but also for effective operation of the immune system (*6*). Alternatively, trade-offs may occur indirectly—for example, intense metabolic activity could lead to immune system damage caused by the release of free radicals (*7*). It has even been suggested that the reduced immunocompetence of males may be an adaptive response, which minimizes the risk that the male immune system will produce autoantibodies, as happens during autoimmunity (*8*). The relative likelihood of these different mechanisms has not yet been established.

It is worth remembering that the sex differences in susceptibility to parasitism may not reflect "maleness" per se. Indeed, Moore and Wilson (*2*) show that, in species where females are larger than males, it is the females that suffer the greater burden of parasitism. In other words, males are not special, they just tend to be big. This counterintuitive result highlights one of the great difficulties in interpreting results based on the incidence of parasitism: Variations between individuals may be due to differences in exposure to parasites rather than differences in resistance to parasites. Thus, in the context of sex differences in parasitism among mammals, males may simply offer a bigger "target" to parasites because they are big and eat a lot. Again, some human studies support this view, with one showing that women were more vulnerable to some nematode infections simply because they did most of the washing and thereby were more frequently exposed to the infective stage of the parasite (*9*).

The next step is to discover more about the precise physiological mechanisms that lead to the unusually high susceptibility of large mammals to parasitic diseases. Is this susceptibility due to a shortage of energy or a scarcity of nutrients, or is it simply because of a greater exposure to the parasites?

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PERSPECTIVES: ECOLOGY

Quaternary Refugia and Persistence of Biodiversity

Pierre Taberlet and Rachid Cheddadi

Preserving biodiversity represents a daunting challenge for human societies. Ideally conservation policies should be based on sound scientific data, including an understanding of the mechanisms that sustain biodiversity over long periods of time. On page 2044 of this issue, Tzedakis *et al.* illustrate the importance of southern refugia for the persistence of some temperate tree species during the last glacial-interglacial cycles (*1*).

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The Milankovitch theory of climates, relates the glacial-interglacial cycles to changes in Earth's orbital parameters during the Quaternary period (the last two million years). These long-term parameters are orbital eccentricity, obliquity, and precession, with periods of 100,000, 41,000, and 19,000 to 23,000 years, respectively (*2*). Superimposed on the long climatic cycles are short and abrupt climate changes caused by the complex relationships between solar energy, vegetation, and the oceans. For example, in the North Atlantic Ocean, cold climatic cycles of about 10,000 to 15,000 years duration correspond to shifts in the ocean-atmosphere temperature (*3*). These short cycles culminate in huge discharges of icebergs into the North Atlantic Ocean (Heinrich events) (*4*) that are followed by an abrupt shift to a warm climate. Both the long-term and the short-term climatic varia-