similar chromosomes); genes that control characters such as spermatogenesis and meiosis should be disabled, deleted, or co-opted for other functions; and transposable elements ought to be disabled or lost (*8*). Finding such characteristics in the bdelloids would dispel any lingering doubt over their claim to be ancient asexuals. More significantly, the different theories of sex make different predictions about what to expect of ancient asexuals. The models in which harmful mutations inexorably exterminate asexual lineages (*9*, *10*) imply that bdelloids might have some extraordinary way of avoiding mutations, perhaps in the form of an as yet undiscovered mechanism of DNA repair (*11*). In contrast, the models in which parasites are the executioners (*12*) would look instead to mechanisms of disease resistance—and the bdelloids have some nasty diseases to resist (see the figure) (*13*). Perhaps the bdelloids have invented a kind of local recombination between a few disease resistance loci. Understanding how the bdelloids defeat these challenges will help us—at last—to discriminate between competing theories of sex.

But, of course, the Class Bdelloidea is just one lineage. Studying bdelloids by themselves, we may never be sure which of their idiosyncrasies are causes of their successful asexuality, which are consequences, and which are merely incidental. Hence the need for a second new line of research, that is, the application of techniques and insights developed in bdelloids (starting with the methods used by Mark Welch and Meselson) to other asexual lineages, both ancient and recent. When we understand the full range of consequences of the loss of sex—the rapid extinction of the many and the enduring survival of the few—we will finally understand why most of us can't do without it.

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PERSPECTIVES: MICROBIOLOGY

# When Being Hyper Keeps You Fit

**Paul B. Rainey and E. Richard Moxon**

Keeping pace with an ever-changing environment is critical to the evolutionary success of all organisms. The key lies in variations in biological characteristics (phenotypic variation) that are determined by regulation of gene expression or mutations in genes. In the case of pathogenic bacteria, the host environment is a particularly stringent test of adaptive potential because the bacteria must cope with precipitous and dynamic changes. On page 1251 of this issue, Oliver *et al.* (*1*) describe their investigations of *Pseudomonas aeruginosa*, a bacterium that in the last 50 years has emerged as one of the most important causes of opportunistic infections in humans. Their crucial finding is that in long-term infections, some strains of *P. aeruginosa*, the mutators, evolve significantly higher rates of mutation. From this they suggest that rapid adaptation of bacterial populations is required to ensure their survival within hosts. If this is correct, then the data of Oliver and colleagues provide compelling evidence for the power of host selection, not merely on the antigens expressed by bacteria, but on the genetic machinery responsible for generating variation.

*P. aeruginosa* is a ubiquitous and remarkably versatile bacterium capable of persisting in soil, water, and in the tissues of plants, humans, and even nematodes. This versatility is consistent with its large genome size and a plethora of regulatory mechanisms that enable the bacterium to co-ordinate metabolic pathways and optimize nutritional and reproductive potential. A prime example of its pathogenic capability in humans is the devastating lung infection that it causes in individuals with the inherited disease cystic fibrosis (CF). Colonization of the human respiratory tract, even when microbial clearance mechanisms are severely compromised as in CF, is a formidable challenge in adaptation for bacterial invaders (see the figure). Frequent fluctuations in the physical structure and physiology of the respiratory tract (caused by inflammation and damage wrought by both innate and acquired immune responses) generate a spatially and temporally complex environment. An additional layer of heterogeneity comes from the imposition of treatment regimes by energetic and determined physicians, who employ a range of measures including the aggressive and multiple administration of potent antibiotics.

The Oliver *et al.* study strengthens the idea that there is more to *P. aeruginosa* variation than the versatility provided through gene regulation. Indeed, it has been recognized for some time that a spectrum of naturally occurring mutations results in overproduction of a protective alginate polymer on the bacterial cell surface, which in turn facilitates adaptation of *P. aeruginosa* to the respiratory tract (*2*). Furthermore, Baquero and others have found that, in the laboratory, *P. aeruginosa* isolates obtained from any individual CF patient show substantial variation in colony phenotype over time, despite possessing the same genetic composition (genotype) (*3*). The possibility that the different variants are adaptive mutants, favored by selection because of their ability to colonize specific niches (*4*) within the respiratory tract, prompts the view that diversification through mutation is a major factor contributing to the fitness of *P. aeruginosa* in the CF lung.

To examine this idea more rigorously, Oliver *et al.* obtained *P. aeruginosa* isolates from the sputum of chronically infected CF patients and also from non-CF patients with acute infections. Remarkably, about 20% of the isolates from CF patients had a mutator phenotype (that is, they had remarkably high mutation rates), whereas, in stark contrast, no such strains were found in isolates from non-CF patients with acute short-term infections. These so-called mutator strains typically have mutations in genes that control DNA metabolism, for example, genes that encode DNA repair enzymes (*5*). To prove that the high mutation rates were the result of mutations in mismatch repair genes, Oliver *et al.* used genetic techniques to replace these defective genes with functional (wild-type) versions. When they did this, the mutation rates reverted back to normal levels.

The scenario emerging from the studies of Oliver and co-workers is that of an arms race between microbe and host, a concept in keeping with the theoretical prediction that

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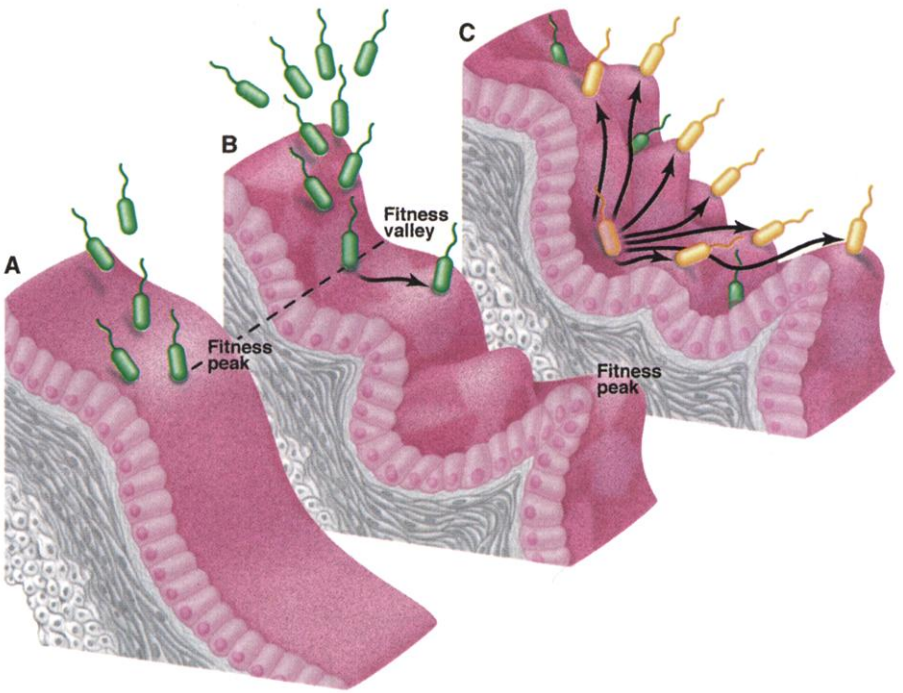
mutators can accelerate the pace of adaptive evolution (*6*). Mathematical models predict that mutators will be selectively favored in rapidly changing environments, provided there is a genetic linkage between the mutator alleles and the beneficial mutations that they cause (as is the case in asexual populations). This prediction is reasonable because an increased supply of potentially beneficial mutations will facilitate adaptation to dynamic changes in the environment (see the figure). Thus, although the possibility that mutators were more likely to colonize the CF lung ab initio has not been rigorously excluded by the investigators, the balance of their evidence does suggest that the mutators evolved within the host.

The potential importance of these findings for the emergence of new traits in bacterial pathogens, especially antibiotic resistance, raises a number of issues. The greater prevalence of mutator populations (found in 11 out of 30 CF patients) in CF respiratory secretions relative to those from patients with acute infections is impressive. However, in addition to issues of sampling bias, the comparison of CF isolates to those from acutely infected patients (although appropriate with respect to the short period of time that the bacteria had spent within the host) may have introduced confounding variables. In particular, isolates from acutely infected patients would be subjected to very different selective pressures compared to those from the compromised respiratory tract of CF patients. Data on the prevalence of mutators from CF patients of different ages and different stages of disease progression would be illuminating, as would results on the frequencies and population dynamics of the mutators themselves. Furthermore, the contribution of mutators to the pathogenesis of the CF lung remains unknown. Although there are compelling reasons to suppose that mutators facilitate adaptation of *P. aeruginosa* populations to the heterogeneous environment of the respiratory tract, mutators must ultimately bear the cost of an elevated mutational load. Their high mutation frequency may not confer any adaptive advantage per se, but may simply reflect genetic linkage between the mutator and a beneficial mutation, resulting in the mutator "hitchhiking" along and thus appearing at a much higher frequency than would be expected. Moreover, mutators—even high-frequency mutators—will have little effect on the pace of adaptive evolution if competition between adaptive mutants is intense (clonal interference) (*7*). That said, the heterogeneous lung environment, in conjunction with population bottlenecks caused, for example, by antibiotics, is likely to limit clonal interference and favor the evolution and persistence of mutators.




**The evolution of mutators.** (**A**) Early in the clinical course of cystic fibrosis (CF), nonmutator *P. aeruginosa* bacteria (green) colonize the respiratory tract of CF patients and a single genotype establishes itself. Inflammation and lung damage are mild, and so rigorous high-dose antibiotic regimens are not given. (**B**) Later in the clinical course of CF, persistent chronic infection and inflammation cause widespread damage to the respiratory tract, resulting in a heterogeneous and rapidly changing "landscape" that poses a stringent challenge to the adaptive potential of *P. aeruginosa*. The bacteria are subjected to further selection by antibiotics, which permeate the lung tissues unevenly, creating concentration gradients ranging from lethal to sublethal (red to pink). Overall, the dynamically changing host environment provides an ecological opportunity that is conducive to rapid divergence (adaptive radiation) of *P. aeruginosa*. (**C**) If some strains of *P. aeruginosa* evolve a high mutation rate (mutators, yellow), they are able to adapt more efficiently to the heterogeneous environment of the respiratory tract through achieving new fitness peaks more rapidly. Antibiotics and host immune responses do not penetrate all tissues uniformly, allowing some opportunistic clones of bacteria to multiply and become predominant in the population.

It has been argued that physicians pay too little attention to ecological and evolutionary factors in the pathogenesis of disease (*8*). The aggressive protocols used to treat CF patients, including cycles of rigorous antibiotic treatment, may drive the population of infecting bacteria into top evolutionary gear and thereby increase the probability of their acquiring new phenotypes, such as heightened virulence. In addition to mutators that result in a global increase in the rate of genetic variation, other mechanisms that facilitate evolution include the site-specific sequences of repetitive DNA (contingency loci) (*9*) found in the bacterial pathogens *Haemophilus influenzae* and *Neisseria meningitidis*.

Microbial persistence in animal hosts is often about survival in the evolutionary fast lane. Alone or in combination, global and localized hypermutation offer substantial increments in adaptive potential. Francois Jacob, the French microbiologist and Nobel laureate, once observed (*10*): "Only in bacteria can speed of growth and size of population allow the organisms to wait for the appearance of a mutation in order to adapt." But microbes that wait too long may be extinguished so their "evolution has become possible only because genetic systems have themselves evolved."

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