dam, 1993), pp. 79–100; D. M. Wood and W. F. Morris, *Am. J. Bot.* **77**, 1411 (1990).
4. M. E. Harmon *et al.*, *Adv. Ecol. Res.* **15**, 1 (1986); C. Maser *et al.*, Eds. *From the Forest to the Sea: A Story of Fallen Trees* (USDA Forest Service General Technical Report PNW-GTR-229, U.S. Department of Agriculture, Washington, DC, 1988); J. F. Franklin *et al.*, *Ecological Characteristics of Old-Growth Douglas-Fir Forests* (USDA Forest Service General Technical Report PNW-GTR-118, U.S. Department of Agriculture, Washington, DC, 1981); T. A. Spies and J. F. Franklin, in *Biodiversity in Managed Landscapes: Theory and Practice*, R. C. Szaro and D. W. Johnson, Eds. (Oxford Univ. Press, New York, 1996), pp. 296–314.
5. J. F. Franklin *et al.*, *Conserv. Biol. Practice* **1**, 1 (2000).
6. See collections of articles in *BioScience* **39**, 678-722 (1989); *Biotropica* **23**, 313–521 (1991); *BioScience* **44**, 224–262 (1994).
7. D. R. Foster *et al.*, *BioScience* **47**, 437 (1997).
8. See for example the selection of articles in *Ecosystems* **1**, 493–557 (1998).
9. K. Kohm and J. F. Franklin, Eds., *Creating a Forestry for the 21st Century* (Island Press, Washington, DC, 1996); J. F. Franklin, in *Ecosystem Management*, M. S. Boyce and A. Haney, Eds. (Yale Univ. Press, New Haven, CT, 1997), pp. 21–53.
10. Ecological research at Mount St. Helens has been supported by the U.S. Department of Agriculture Forest Service Pacific NW Research Station and the NSFO. We are grateful for helpful comments from V. H. Dale, P. Frenzen, and F. Swanson on this Perspective.

PERSPECTIVES: EVOLUTIONARY GENETICS

Sinless Originals

Olivia P. Judson and Benjamin B. Normark

Is it possible to live without sex for millions of years? That depends on what you mean by "sex." Certainly most organisms do fine without copulation. But if by sex you mean swapping DNA between genomes, then that is much harder to forgo. Among eukaryotes, the cycle of meiosis (in which the genome is split into random halves) and syngamy (in which shuffled half-genomes are fused into new wholes) seems to be essential. Asexual organisms—creatures in which this cycle has come to a stop—are widely thought to be doomed to a swift extinction (*1*). The apparent exceptions to this rule—those few ancient and diverse lineages of organisms in which sex is unknown (*2*)—are regarded with suspicion. Time and again, evidence of sex has been found in supposedly ancient asexual lineages (*2*), and many evolutionary biologists do not believe that any of the apparent exceptions are real (*3*, *4*).

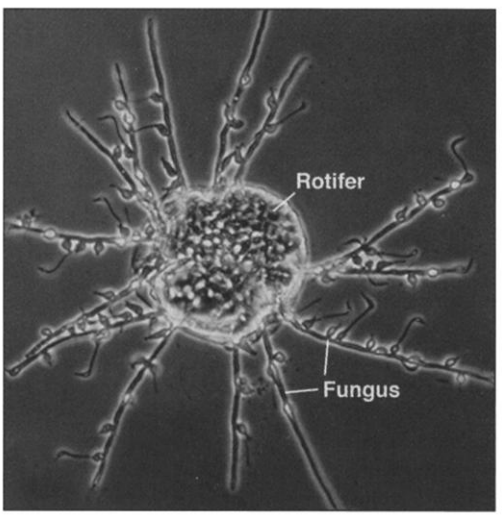
Although evolutionary biologists agree that sex is essential, they cannot agree why. More than 20 hypotheses, ranging from the sublime to the ridiculous, have been advanced to explain why sex is crucial for evolutionary success (*5*). Two factors have abetted this exuberant proliferation of ideas. First, an evolutionary explanation for the success of sexual reproduction would bridge a huge hole in the theoretical basis of modern biology. Second, the debate has taken place in the absence of decisive data.

But help is on the way. On page 1211 of this issue, Mark Welch and Meselson (*6*) present robust evidence that the most celebrated of the apparent exceptions to the rapid-extinction rule—the rotifers of the Class Bdelloidea—are exactly what they appear to be: a diverse and successful group of invertebrates that thumb their noses at evolutionary theorists by having lived entirely without sex for at least 40 million years. At the same time, their work lays the foundations, and provides the essential tools, for two new avenues of research.

As Meselson was the first to realize, an organism that has truly been without sex for millions of years should show a distinctive and peculiar genomic structure and pattern of DNA-sequence relationships. From the moment meiosis ceases, the genome essentially freezes, with any subsequent changes arising mostly as a result of mutation. Pairs of gene sequences that were once alleles should start to accumulate mutations independently, and hence to diverge from one another. A clade that diversified after an ancient genome freeze should therefore show unprecedented levels of heterozygosity. If you pick two alleles at any locus within a single individual, the sequences should show consistent and extreme divergence, because they will have been diverging ever since the genome froze. But, curiouser and curiouser, the common ancestor of any two extant individuals will be more recent than the genome freeze. Hence, if you compare alleles *between* even very distantly related individuals, you should find that they are frequently less divergent from each other than are the two alleles *within the same individual*. This weird pattern of DNA-sequence relationships is precisely what Mark Welch and Meselson have found.

In some ways a genome freeze is analogous to a genome duplication: Every copy of every gene suddenly becomes an independent locus in the sense that it evolves entirely independently of its homolog and former meiotic partner. It is possible that the results of Mark Welch and Meselson reflect an ancient genome duplication rather than an ancient loss of meiosis. But to explain their results this way you must also invoke a second hypothesis: that coincident with genome duplication the bdelloids lost virtually all heterozygosity by some unknown mechanism. In principle, complete homozygosity could be maintained by automixis (meiosis and fusion of cells from a single individual), although there is no cytogenetic evidence for that. It is even possible that the bdelloids represent the haploid phase of a life cycle whose diploid phase remains to be discovered, although such a life cycle would be unique among animals. But these are thin straws to clutch at: The striking DNA sequence relationships that Mark Welch and Meselson have discovered are exactly those predicted for an ancient asexual clade and are consistent with the often-stated a priori hypothesis that the bdelloid rotifers abandoned sex millions of years ago (*7*).

What now? The first, and most pressing, program of research must focus on the bdelloids themselves. A number of dramatic predictions that flow from the hypothesis of ancient bdelloid asexuality have yet to be confirmed: The extreme heterozygosity reported for a few loci by Mark Welch and Meselson should apply to the entire genome, such that each chromosome has a unique size and gene order (as against being one of a pair of very



Under attack. A bdelloid rotifer (Phylum Rotifera, Class Bdelloidea) in the final stages of succumbing to attack by one of its parasites, the fungus *Harposporium angularis*. Parasites are thought to be one of the forces maintaining sex in populations.

CREDIT: GEORGE L. BARRON

O. P. Judson is in the Department of Biology, Imperial College at Silwood Park, Ascot, Berks SL5 7PY, UK. B. B. Normark is at the Museum of Comparative Zoology, Harvard University, 26 Oxford Street, Cambridge, MA 02138, USA. E-mail: o.judson@ic.ac.uk, bnormark@oeb.harvard.edu

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.

References

1. C. D. Darlington, *Evolution of Genetic Systems* (Cambridge University Press, Cambridge, 1939).
2. O. P. Judson and B. B. Normark, *Trends Ecol. Evol.* **11**, 41 (1996).
3. L. D. Hurst, W. D. Hamilton, R. J. Ladle, *Trends Ecol. Evol.* **7**, 144 (1992).
4. T. J. Little and P. D. N. Hebert, *Trends Ecol. Evol.* **11**, 296 (1996).
5. A. S. Kondrashov, *J. Hered.* **84**, 372 (1993).
6. D. Mark Welch and M. Meselson, *Science* **288**, 1211 (2000).
7. J. Maynard Smith, *The Evolution of Sex* (Cambridge Univ. Press, Cambridge, 1978).
8. D. A. Hickey, *Genetics* **101**, 519 (1982).
9. H. J. Muller, *Mutat. Res.***1**, 2 (1964).
10. A. S. Kondrashov, *Nature* **336**, 435 (1988).
11. I. Schön and K. Martens, *J. Nat. Hist.* **32**, 943 (1998).
12. J. Jaenike, *Evol. Theory* **3**, 191 (1978).
13. G. L. Barron, *Can. J. Bot.* **63**, 211 (1985).

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

P. B. Rainey is in the Department of Plant Sciences, University of Oxford, South Parks Road, Oxford OX1 3RB, UK. E-mail: prainey@molbiol.ox.ac.uk E. R. Moxon is at the Institute of Molecular Medicine, University of Oxford, Headington, Oxford OX3 9DS, UK. E-mail: Richard.Moxon@paediatrics.oxford.ac.uk