On the Origin of Sexual Reproduction

For Darwin, sex was a big question mark. "We do not even in the least know the final cause of sexuality; why new beings should be produced by the union of the two sexual elements," he wrote in 1862. "The whole subject is as yet hidden in darkness."

Today, biologists understand the molecular nuts and bolts of sex fairly well. Each new human being (or bird or bee) needs a set of chromosomes from each parent. But that's the *how*. The *why* of sex is still fairly mysterious. Bacteria don't have to search for a mate; they just grow and divide in two. An aspen tree can simply send out shoots that grow into new trees. No muss, no fuss with finding a partner, fertilizing an egg, and joining two genomes. Why should so many species take such a labyrinthine path to reproduction, when straightforward routes are available?

Biologists first began to give the question "Why sex?" serious attention about 40 years ago, and today they're using genomics and other 21st century tools to search for the answer. They are finding hidden signs of sex in the DNA of supposedly asexual organisms and are tracking the evolutionary impact of sex among living populations of animals and plants. Some use sophisticated mathematical models to assess the conditions under which sex can arise.

These efforts are providing new hints about how sex first emerged some 2 billion years ago and about the forces that have made it so widespread. The studies bolster a handful of hypotheses: Sex may speed up evolution, for example, or it may provide a better defense against parasites. In the past, scientists have focused on just one of these hypotheses at a time, but today many argue that several forces may be at work at once.

Mating of molecules

Sex gives nature much of its spice. Fireflies flash through the night to find a mate; a flower's perfume lures insects to carry pollen to distant partners; male bullfrogs croak to impress females. But despite this dizzying diversity, all sexually reproducing organisms take the same key steps to make new offspring: They shuffle their own DNA and then combine some of it with the DNA of another member of their species to produce a new genome. The key to this novelty is a process called meiosis.

As with those of other vertebrates, almost all human cells are diploid: Each one contains two copies of very similar, or homologous, chromosomes. As precursor sex cells divide, they give rise to haploid sex cells of sperm and eggs, each with only one chromosome from each pair. Only when one sex cell fuses with another does it become part of a new diploid genome.

Meiosis creates new variations in two ways. There's a 50-50 chance that a parent will pass down either chromosome of a given pair to his or her offspring. And during the development of sex cells, homologous chromosomes undergo recombination: They line up with each other and swap segments of their DNA. So even if two siblings get the same chromosome from their mother, their chromosomes aren't identical.

In 1971, the late British evolutionary biologist John Maynard Smith helped kick off the modern study of the evolution of sex by pointing out how costly sons are to a mother. An asexual female lizard, for example, produces just daughters, all of whom can reproduce. A sexually reproducing female lizard, on the other hand, produces, on average, a son for every daughter, half the reproductive potential. Yet despite this "twofold cost of sex," as Maynard Smith called it, he observed that sex is widespread, as most animals and plants produce males and females.

And he didn't even realize how widespread sex is. It's starting to seem as if just about all eukaryotes—the lineage that includes animals, plants, fungi, and protozoans—have some sort of sex. (Fungi and protozoans don't have males and females like we do; instead, they produce two or more "mating types.") In April, for example, signs of sexual recombination were discovered in the seemingly asexual *Leishmania*, a protozoan that causes the tropical disease leishmaniasis (*Science*, 10 April, pp. 187, 265).

Other asexual eukaryotes show signs of having evolved from sexual ancestors. *Trichomonas vaginalis*, a protozoan that causes vaginal infections, doesn't appear to reproduce sexually, for example. But in 2007, John Logsdon of the University of Iowa in Iowa City and his colleagues discovered that its genome contains almost all the genes necessary for meiosis, suggesting that it was once a sexual creature. Given how widespread sex and sex-related genes are, Logsdon says, "it's hard to escape the conclusion" that sex first evolved in the common ancestor of all eukaryotes some 2 billion years ago.

The road to sex

In trying to understand how this transition occurred, most scientists thought that meiosis and sex evolved together, as a package. But Adam Wilkins of the University of Cambridge in the United Kingdom and Robin Holliday of the Australian Academy of Sciences have recently argued that some key steps in meiosis—namely, the reduction of diploid cells into haploids—took place long before full-blown sex existed. "It turns the conventional thinking on its head," says Wilkins.

Wilkins and Holliday's scenario starts with the ballooning of the genomes of the early, asexual eukaryotes. Although the most ancient single-celled, amoebalike creatures were probably haploid, like modern bacteria, today the eukaryote genome can be thousands of times the size of a bacterial one, and many studies suggest that it was inflated billions of years ago by invading viruslike segments of DNA called mobile elements.

At first, these early eukaryotes reproduced simply by duplicating their giant haploid genomes and dividing. But at some point, Wilkins and Holliday propose,

THE YEAR OF DARWIN

This essay is the sixth in a monthly series. For more on evolutionary topics online, see the Origins blog at **blogs.sciencemag.org/origins**. For more on sexual reproduction, listen to a podcast by author Carl Zimmer at **www.sciencemag.org/multimedia/podcast**.

CREDITS: DEA PICTURE LIBRARY/GETTY IMAGES; WIKIPEDIA/GEORGE RICHMOND, FROM ORIGINS, RICHARD LEAKEY AND ROBERT LEWIN

Downloaded from www.sciencemag.org on December 3, 2009

Published by AAAS

diploid cells arose. Two haploid cells might have fused, for example, or a cell may have failed to divide after duplicating its DNA. Today, some fungi pass through these kinds of diploid stages.

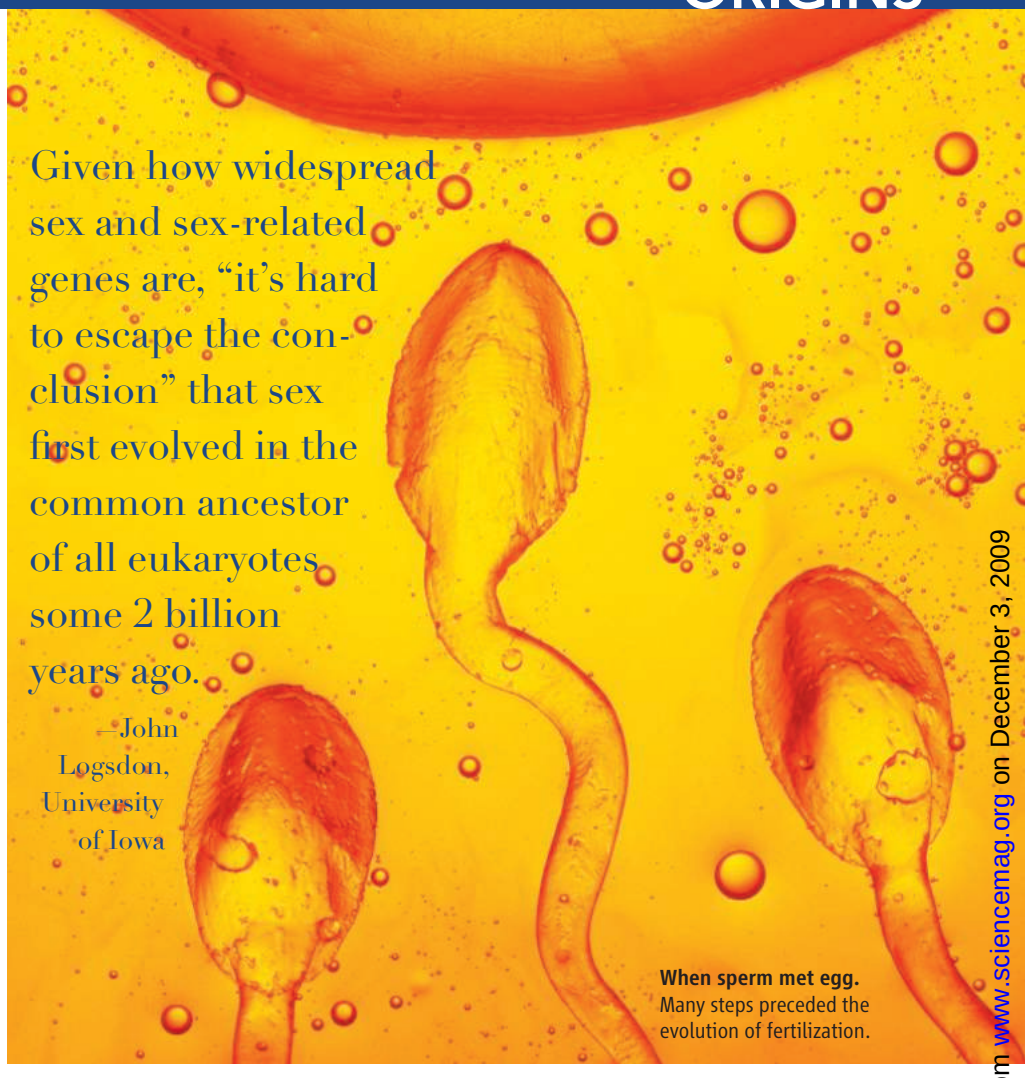
The combination of a big genome and a new diploid stage raised the risk that eukaryotes would make fatal mistakes while copying their DNA. A chromosome can potentially join any other chromosome wherever they share similar sequences. It's safe for this to happen between homologous chromosomes, because they will swap versions of the same genes during recombination. But when one chromosome recombines with a nonhomologous chromosome, "that leads to terrible problems," says Wilkins. Each chromosome donates some of its genes but doesn't get the same genes back. A cell that inherits one of these deficient chromosomes may die.

Wilkins and Holliday argue that this risk drove the evolution of a new defense. In one or more lineages of early eukaryotes, homologous chromosomes began to line up tightly with one another before cells divided. Now recombination could take place safely. If a chromosome swapped some of its genes with another chromosome, it would get versions of the same genes back. Meiosis thus evolved as a way to reduce the damage from mismatched recombinations.

It would take millions of years more before eukaryotes shifted from a mostly haploid existence to spending most of their life cycle as diploids (as we do) and only sometimes producing the haploid cells necessary today for sexual reproduction. That shift to a sexual life cycle, however, still had to overcome the twofold cost of sex.

Lilach Hadany of Tel Aviv University in Israel and Sarah Otto of the University of British Columbia, Vancouver, in Canada, have been building mathematical models to explore the evolutionary pressures that might have allowed a population of asexual eukaryotes to become sexual. They find that sex can come to predominate if it's only optional.

Hadany and Otto created a mathematical model of eukaryotes in which most of the organisms were asexual, but some carried genes that let them reproduce sexually when under stress. This reflects real life: Today, yeast and many species of plants reproduce sexually only during times of stress and reproduce asexually the rest of the time. The researchers found that over the generations, from one crisis to the next, the sex genes spread. By triggering organisms to reproduce sexually, these genes could become combined with new sets of genes that were better able to withstand the crisis, leading to the greater proliferation of the "sexual" individuals. Once the crisis was over, the sex genes turned off, allowing the advantageous combinations of genes to remain intact.



When sperm met egg. Many steps preceded the evolution of fertilization.

CREDIT: DENNIS WILSON/CORBIS

However, this strategy "doesn't happen because sex is good for the population," Hadany points out. Instead, the model suggests that genes for sex spread thanks to their own selfish drive to generate ever more copies of themselves.

If sex started out as an optional way to reproduce, then a new question emerges: How did sex later become mandatory in many species, including our own? Hadany suspects that the answer has to do with sexiness—that is, with the preference sexually reproducing organisms often have to mate with some individuals over others. Female guppies, for example, like to mate with male guppies with bright spots; in some frog species, the females choose to mate with the males that croak loudest.

Hadany and Tuvik Beker, then at Hebrew University of Jerusalem, built a mathematical model in which the frequency of sex as well as the mating preferences could evolve. Under these conditions, they found, the population evolved to reproduce sexually more and more often until asexual reproduction ceased all together. The sexy individuals were driving this evolution. Because they could attract so many more mates from the opposite sex, they could have more offspring through sexual reproduction than by just cloning themselves. (The female's advantage comes in part from sexy sons that achieve reproductive success through mate preference.) As a result, mutations that increased the amount of sex increased these organisms' success. These genes passed down to more offspring and eventually spread through the entire population.

Here to stay

Although sexiness may help explain how sexual reproduction took over, it can't fully explain why sex has managed to reign for billions of years. Because they don't have to pay the twofold cost of sex, under the right conditions, any new cloners ought to spread rapidly in a population, challenging sexual reproduction. However, given the rarity of asexuals, something must be getting in the way. Over the years, scientists have proposed about

Downloaded from www.sciencemag.org on December 3, 2009

Published by AAAS

20 different hypotheses to explain the failure of asexuality to regain much of a foothold. Logsdon calls the three with the most support from both experiments and mathematical analysis "the good, the bad, and the ugly."

The "good" refers to the ability sexual species have to adapt faster than asexual ones. If an asexual organism picks up a beneficial mutation, it can only pass the mutation down to its direct offspring. If another organism picks up a different beneficial mutation in a different gene, then there's no way for it to be combined into the same genome as the first mutation to make a more optimal genome. Sexual reproduction, on the other hand, splits up genes and recombines them into new arrangements, joining beneficial mutations.

In this way, sexual reproduction may improve the fitness of a population faster than asexual reproduction. In 2005, Matthew Goddard and colleagues at the University of Auckland in New Zealand genetically engineered some yeast that could only reproduce sexually and others that could only reproduce asexually. (Typically, yeast can do both.) When Goddard raised both mutants on a near-starvation diet, the sexual yeast were able to adapt faster. As they evolved, their growth rate increased 94%, while the asexual strain increased only 80%. The difference in growth would allow the sexual yeasts to rapidly take over a population.

Oh, how sexy. That animals as diverse as (*left to right*) guppies, peacocks, and dung beetles are picky about their mates may help ensure that sexual reproduction prevails.

The "bad" refers to slightly harmful mutations and what sex does to purge them. Over time, a population of asexual organisms may pick up mutations that slow their growth rate. Each mutation may be only slightly deleterious, and so natural selection fails to eliminate it from the population. As generations pass, more and more harmful mutations accumulate, dragging down the expansion of the population. Eventually, these slightly deleterious variants may replace all the undamaged versions of these genes in a population, permanently compromising fitness. Sexual organisms, on the other hand, can trade in a defective version of a gene for a working one through recombination, keeping healthy genomes intact.

Real examples that celibacy can be bad for the genome exist. In 2006, for example, Susanne Paland and Michael Lynch of Indiana University, Bloomington, looked at mutations in *Daphnia pulex*, a species of water flea. Populations of asexual water fleas carried more harmful mutations than sexual ones.

Along with the "good" and the "bad," there is the "ugly": namely, parasites, against which sex may be a powerful defense. In the 1970s, several researchers built mathematical models of how parasites influenced the evolution of their hosts and vice versa. Their research suggested that both partners go through cycles of boom and bust. Natural selection favors parasites that can infect the most common strain of host. But as they kill off those hosts, another host strain rises to dominate the population. Then a new parasite strain better adapted to the new host strain begins to thrive, leaving the old parasite strain in the dust.

This model of host-parasite coevolution came to be known as the Red Queen hypothesis, after the Red Queen in Lewis Carroll's book *Through the Looking Glass*, who takes Alice on a run that never seems to go anywhere. "Now *here*, you see, it takes all the running *you* can do to keep in the same place," the Red Queen explains.

The Red Queen conundrum, some researchers have argued, may give an evolutionary edge to sex. Asexual strains can never beat out sexual strains, because whenever they get too successful, parasites build up and devastate the strain. Sexual organisms, meanwhile, can avoid these dramatic booms and busts because they can shuffle their genes into new combinations that are harder for parasites to adapt to.

Red Queen models for sexual reproduction are very elegant and compelling. But testing them in nature is fiendishly hard, because biologists need asexual and sexual organisms that share the same environment and parasites. One of the few test cases scientists have found is *Potamopyrgus antipodarum*, a snail that lives in New Zealand lakes. Some snails have to mate to reproduce; others don't.

Curt Lively of Indiana University, Bloomington, and his colleagues have spent nearly 30 years painstakingly studying the snails and one of their parasites, a fluke that can sterilize them. In a paper in press at *The American Naturalist*, Lively and collaborators Jukka Jokela of the Swiss Federal Institute of Aquatic Science and Technology and Mark Dybdahl of Washington State University, Pullman, present some of the most compelling evidence gathered so far for the Red Queen at work.

Over the course of the past 15 years, Lively and his colleagues have documented a parasite-driven boom-and-bust cycle in asexual snails, a cycle just as the Red Queen would predict. In a New Zealand lake in 1994, the most common strains of asexual snails were initially resistant to the most common flukes. Over time, the snails became more and more vulnerable, as a well-adapted fluke strain infected them. By 2004, the snails had all but disappeared. Meanwhile, a rare strain of asexual snails in 1994 became the most common, apparently because it was resistant to the fluke strain sickening the previous dominant strain of snails. "We didn't expect to see such a dramatic shift in our lifetimes," says Lively.

As the flukes drove the asexual snails through boom and bust, the population of sexual snails has remained relatively steady, Lively says. That stability is consistent with the idea that the Red Queen effect can give sexual organisms an edge.

Yet Lively doesn't think that the Red Queen on its own can fully account for the staying power of sex. Once an asexual strain of hosts becomes rare, its parasites become rare, too. So the Red Queen can't wipe out asexual reproduction altogether.

It's possible that the Red Queen may be able to work more effectively to promote sex by cooperating with another force. For example, the Red Queen may drive asexual populations down to small numbers, which may make it easier for harmful mutations—the "bad"—to build up.

"There are a lot of people who don't like this fusing of hypotheses," admits Lively. "It gets messy, and it gets hard to test." Yet Lively and some other researchers think that messiness is no reason to reject the possibility that sex has many masters. It won't be surprising if a mystery so hidden in darkness turns out to have more than one answer. **–CARL ZIMMER**

Carl Zimmer's latest book is *Microcosm: E. coli and the New Science of Life*.

CREDITS: JUPITERIMAGES

Downloaded from www.sciencemag.org on December 3, 2009

Published by AAAS