The Evolution of Sexes

Two Oxford biologists argue that selfish genes explain why human beings and many other organisms come in just two sexes

In science, it's the simple questions that generally turn out to be hardest to answer. Take that basic question that 4-year-olds are fond of asking: "Why are there boys and girls?" You might think you've got the answer in terms of mothers and fathers and storks and babies. But think again: That's an answer to the question of why there is sex, but what the 4-year-old is asking is why there are separate sexes. So let's make the question a little clearer: Try explaining why human beings come in two sexes, instead of three or four or five or even none!

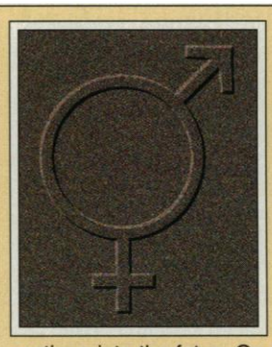
Start thinking about this question, and you'll soon realize that having two sexes is an odd arrangement. If the purpose of one sex meeting the other is to combine DNA, what could be worse than having two sexes? Any one individual can choose a partner from only 50% of the population, meaning valuable time must be wasted in tracking down a mate. Given that, biologically speaking, the only people you don't want to mate with are close relatives, wouldn't it be far better to have say, 20 sexes, with the rule that you can mate with any partner except one of your own sex? Let "boy seeks girl" be replaced with "sex type 18 seeks any nonself" and no more lost time—95% of the population can be viewed as potential partners.

Like other big, simple questions, the problem of why there are but two sexes (at least among higher organisms) is one that most biologists have passed by in blissful ignorance. Not so the University of Cambridge's Ronald Fisher, the founding father of modern population genetics. "No practical biologist interested in sexual reproduction would be led to work out the detailed consequences experienced by organisms having three or more sexes," he wrote in his monumental 1958 work *The Genetical Theory of Natural Selection*, "yet what should he do if he wishes to understand why the sexes are, in fact, always two?"

Now Fisher has his answer. The "practical biologist" should turn to the March issue of the *Proceedings of the Royal Society of London*. There a young Oxford University evolutionary biologist named Laurence Hurst, working with veteran William D. Hamilton, has put together a model that sees the evolution of separate sexes as a form of genomic "conflict management." Hurst and Hamilton argue that this conflict management is essential among those organisms—from unicellular algae to human beings—that reproduce by fusing two cells, so bringing together both the genetic material in the nuclei and that in cytoplasmic organelles like mitochondria and chloroplasts.

Combined with empirical evidence culled from the mating habits of a miniature Noah's Ark of obscure creatures—including one that breaks the rules by having at least 13 sexes—the thesis explains, says Hurst, "why if you are going to fuse, there should be sexes, and if there are sexes, why the number of them is usually likely to be two."

So far, the Hurst and Hamilton paper has had a good reception. For evolutionary biologists who've seen similar speculative ideas about the sexes come and go, empirical evidence is what counts. And on that standard, says John Maynard Smith, professor of biology at the University of Sussex, "it's very convincing." He was impressed, it seems, by some of the more unusual creatures that test Hurst's thesis. Rolf Hoekstra, a professor of population genetics at the University of Wageningen in Holland who tackled the problem while in Maynard Smith's laboratory several years ago, is also impressed. "The issue of why are there two sexes has always been a bit esoteric because it's so very hard to find the empirical backing for an idea," he says. "Their [Hurst and Hamilton's] explanation is the most attractive we have because of their addition of this nice empirical correlation."

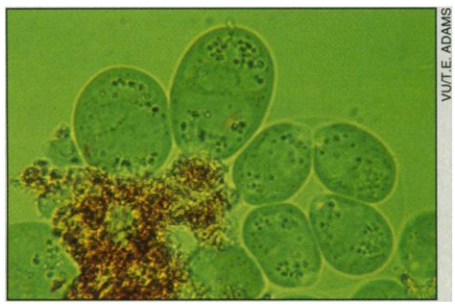


The Sexes and Sexual Selection

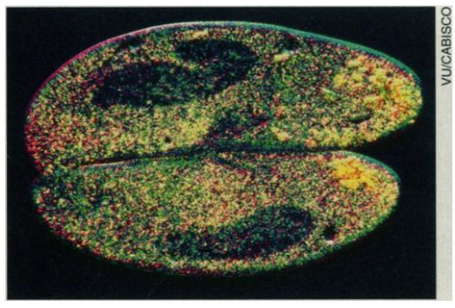
In this package of articles, *Science* reviews some of the new ideas and data that have appeared recently from researchers studying the evolutionary biology of sex. Beginning on this page, we tackle some of the problem of sexes, asking first why separate sexes evolved in the first place, and then (p. 325) showing how the battle of the sexes may continue into the fetus. On page 327, Matt Ridley reports on a new theory about how the swallow got its long, forked tail; the theory may explain what it is that females are looking for in a male—if they are birds, that is. For primates, the situation is a lot more complicated: On page 329, Ann Gibbons charts the latest difficulties for theories explaining how primates select their mates.

Intracellular warfare

The roots of Hurst's hypothesis lie in the field of "intragenomic conflict," a hot new research area among Oxford's evolutionary biologists. The traditional view of the interior of the cell is one of a miniature Gaia, with all the genetic elements—the chromosomes, mitochondria, and other cytoplasmic



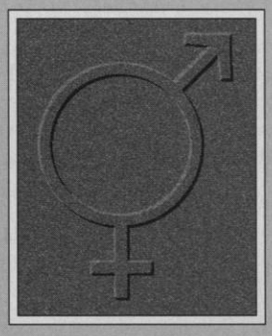
A fuser. *Chlamydomonas* reproduces by cell fusion and has two sexes.



A conjugator. *Paramecium* doesn't exchange organelles and does not have separate sexes.

A rule-breaker. Slime molds have 13 sexes, but is this arrangement stable?

Fetal Development and the Battle of the Sexes



If Australian geneticist David Haig is right, genetic conflict during the process of reproduction didn't end with the evolution of males who unilaterally give up their organelles (see main text). Haig argues that the battle of the sexes carries on into the mammalian fetus developing in the womb. The reason: The nucleus of every cell of the fetus contains DNA from both the mother and the father—but the interests of those two sets of genes can differ. Consider the evolutionary implications of that "intragenomic conflict," says Haig, and you may have an explanation for the strange phenomenon of genomic imprinting—one of the hottest and most puzzling areas of molecular genetics. And that's not all: Haig—currently moving from Oxford to Harvard— argues that some of the complications of human pregnancy can be seen as stemming from intragenomic friction within the cells of the fetus.

The notion that genes within a nucleus behave differently according to their parental origin runs counter to the classical view of human genetics. Until recently, geneticists have assumed that once chromosomes from the sperm and egg paired up in the diploid genome of the developing embryo, the two sets of DNA worked together and equally. But in the past few years, that assumption has been shattered as researchers have found that several human genetic diseases develop according to which parent provides the mutant gene (*Science*, 31 May 1991, p. 1250). One example of such genetic imprinting is a deletion on chromosome 15 that causes Prader-Willi syndrome (characterized by mental retardation and small hands and feet) if inherited from the mother and a different condition, Angelman syndrome (characterized by a more severe form of mental retardation and a large mouth and red cheeks), if inherited from the father.

At the molecular level, inherited patterns of DNA methylation and chromatin structure likely determine which genes are expressed. But ask why such differences evolved in the first place and you're in the dark and Machiavellian world of intragenomic conflict: Differences in maternal and paternal gene expression, says Haig, reflect the differing interests of the maternal and paternal DNA.

Put simply, the chief interest of the paternal DNA is to maximize the development of the fetus, which will perpetuate the father's genes. "The heavier the birth weight of the fetus, the more likely the fetus is to survive and reproduce and pass on copies of its own genes once it has grown to adulthood," explains Haig. Maternal DNA, in contrast, has to think of more than just this one fetus—it has an additional interest in safeguarding the mother's health so that more copies of the mother's genes can appear in future fetuses. A big birth weight, says Haig, means that the mother has less resources to fight off disease—and ultimately, "less resources to expend on future brothers and sisters." The result, says Haig, is "the evolution of a conflict within the fetus with paternal genes demanding more from the mother because they have a smaller interest in the mother's future reproduction."

That may sound like a cynical view, but Haig has good evidence that maternal and paternal genes may behave differently because it's in their own selfish interests to do so. His key example comes from a system that regulates fetal growth in the mouse. In this system, the *IGF-II* (insulin-like growth factor II) gene codes for a potent growth factor that binds to the type-1 IGF receptor and signals cells to divide. More IGF-II means higher growth rates—and sure enough it turns out to be the paternal DNA that drives production of IGF-II. When Thomas De Chiara, a molecular geneticist at Columbia University, disrupted the two genes separately, he found that the gene is expressed only on paternal DNA, while the maternal gene remains silent—mouse embryos inheriting a mutant *IGF-II* gene from their fathers grow up smaller than usual, while those inheriting the same mutation from their mothers are unaffected.

A further twist to the story adds evidence that maternal and paternal DNA are really in conflict over the level of IGF-II. IGF-II also binds to a second receptor, the type-2 IGF receptor—a protein that has been shown to be the same as the mannose-6-phosphate receptor—but in this case binding does not appear to stimulate growth. When the pattern of expression of this receptor gene is examined, it turns out to exactly the reverse of that for the *IGF-II* gene: The gene for the mannose-6-phosphate receptor is expressed in DNA from the mother but not in DNA from the father. Only the maternal gene for the mannose-6-phosphate receptor is switched on, says Haig, because maternal DNA is trying to boost production of the receptor in an effort to mop up IGF-II produced by the paternal DNA. That way, it can prevent the IGF-II from stimulating growth.

The end result of this tug-of-war with the paternal DNA trying to produce as much growth-stimulating IGF-II as possible and the maternal DNA trying to remove it, says Haig, is that the fetus ends up in much the same situation as if the battle had never taken place. That's why it takes a mutation to reveal the presence of genomic imprinting. Put a mutation in either of the maternal or paternal genes, and it's equivalent to letting one end of the rope go: A genetic disease emerges, and its form differs according to whether the maternal or paternal gene was knocked out.

David Haig

Haig is now assembling other examples that he hopes to weave into a broad pattern of evidence to support his hypothesis that maternal-paternal genetic conflict can explain the evolution of genomic imprinting. He's already published a short review in *Cell* (22 March 1991, p. 1045), and he recently followed that up with a more detailed work in *Philosophical Transactions of the Royal Society* (**333**, 1, 1992). Now he's putting together a large review of maternal-fetal conflict in human pregnancy that, he says, "will explain how a perspective of genetic conflict helps to understand some of the medical complications of pregnancy." But Haig is aware that the implications of his thesis may be unsettling to some: "I'm not denying mothers and babies may love each other," he said in a recent radio interview, "we are just talking about the mechanics of how at a biochemical level, the maternal-fetal relationship is organized."

–A.A.

Additional Readings

T. Moore and D. Haig, "Genomic Imprinting in Mammalian Development: A Parental Tug-of-War," *Trends in Genetics* **7**, 45 (1991).

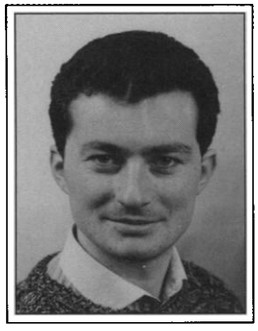
D. Haig and M. Westoby, "Parent-Specific Gene-Expression and the Triploid Endosperm," *American Naturalist* **134**, 147 (1989).

D. Haig and C. Graham, "Genomic Imprinting and the Strange Case of the Insulin-Like Growth Factor II Receptor," *Cell* **64**, 1045 (1991).

organelles—working peacefully together for the common good. The Oxford school, on the other hand, sees a miniature Wall Street where all self-replicating entities are selfishly looking out for themselves.

Look at the conflicting interests within a cell in this way, and there could be a big problem when two cells fuse during sex, says Hurst: Nuclear DNA from each cell comes together into two pairs of chromosomes, but there is a risk of war breaking out between the two sets of organelles, which do not join up and have no reason to share the cytoplasm with the other. All it takes is the emergence of a murderous mutant mitochondrion—and there is good evidence that mitochondria can actively degrade one another with restriction enzymes—or a killer chloroplast, and every mating turns into mayhem.

"If you are going to fuse, there should be sexes. And if you have sexes, you're best off with two."
–Laurence Hurst



Enter Hurst's model for the evolutionary development of sexes. Such is the potential damage to the cell from these battles, explains Hurst, that sexes become essential to avoid conflict between organelles. Put simply, in a two-sex system, one sex (the male or – type) unilaterally disarms and surrenders its organelles, never passing them on to the next generation, while the other sex (the female or + type) enjoys the right of perpetual inheritance for its organelles. Thus, human beings and other animals have evolved so that males produce tiny sperm, which contribute no mitochondria to the zygote, and females produce large eggs, which have been exercising their right to hand down organelles long before Eve appeared in Africa—or Asia, if you prefer.

Put in more precise genetic terms, Hurst's model shows that a nuclear gene that unilaterally destroys its own mitochondria to avoid a costly battle (plus a gene that chooses mates of opposite type—to avoid two disarmers meeting and ending up with no organelles) can go to fixation under realistic evolutionary assumptions.

Exotic sex lives

The model would probably have attracted attention only as a curiosity except that Hurst has, he says, a habit "of browsing through obscure journals in the hope of finding something interesting." As it turned out, all the data he needed for a broad test of his thesis was already lying in the zoological literature, including the one bizarre exception to his rule: the slime mold with 13 or more sexes.

Hurst's expeditions through often obscure and old journals revealed that creatures that have sex can be divided into two key types: those that fuse cells during mating and those that reproduce without cell fusion, passing only nuclei between them. From this observation comes Hurst's big prediction: Only organisms in the first group should have evolved true "sexes" because it is only these creatures that risk warfare between cytoplasmic organelles. Organisms in the second group will have no need for separate sexes because organelles from separate cells are never thrown together.

How does real life bear out this prediction? The common green algae *Chlamydomonas* provides an example in the first category. When it fuses with a partner it shares its nucleus, cytoplasm, and all. Just as predicted, it has two sexes, a + type and a – type. And once again, just as predicted, only the + type's chloroplast is inherited.

The ciliates and the basidiomycetes fall into the second category. Take *Paramecium*, a typical ciliate: During mating, two *Paramecia* pair up alongside one another, but they don't fuse. Instead, explains Hurst, they "open a tiny little hole between them and exchange a micronucleus—they get the advantage of exchanging nuclei, but cytoplasmic genes don't move between them."

As predicted, ciliates like *Paramecium* do not have separate sexes. Instead, freed from the need to worry about strife between cytoplasmic genes, ciliates have dozens of nuclear mating types, ensuring that they can mate with any other member of the species that is not too genetically similar to themselves. The story is broadly similar in the basidiomycetes (mushrooms). Once again, only nuclei are exchanged when the mycelia of two individuals come together, and once again there are many nuclear, "incompatibility types," to avoid inbreeding, but no separate sexes.

So far so good, but what seems to nail down Hurst's pattern is one especially eccentric creature. Digging around in an old copy of the *Journal of Science of Hiroshima University*, Hurst found a paper from zoologist Tadao Takahashi showing that species of hypotrich ciliates are able to perform either fusion sex (when both nuclei and cytoplasm are combined) or conjugatory sex (when only nuclei are exchanged). The neat twist is that, just as predicted, during fusion sex the hypotrich ciliates appear to have just two sexes, while for conjugatory sex they have multiple mating types.

Too many sexes

But what about the 13-sex slime mold? "I was a bit depressed when I read about *Physarum polycephalum*," Hurst says. However, it turns out that slime molds have cracked the mitochondrial conflict problem in a different way—instead of having a hierarchy of two sexes, one of which gives up its organelles, it has a hierarchy of 13 sexes, each one of which has to give way to the one above it. "You have a system of at least 13 alleles in a hierarchical order, so if you have gene number 13 and you mate with anyone else, your cytoplasmic genes will be inherited; but if you have gene number 12, then your cytoplasmic genes will be inherited only if you mate with a partner bearing gene 11 or below," explains Hurst.

The system doesn't challenge the basic idea that uniparental inheritance of cytoplasmic genes is the key to understanding the sexes, but it "reopens the question of why there are usually two sexes," says Hurst: If slime molds can have 13 sexes, giving them the double advantage of avoiding cytoplasmic gene conflict while enjoying the freedom of choice given by multiple mating types, why not other organisms?

Hurst's answer is that it is easy to imagine what could go wrong with 13 sexes arranged in a hierarchy: "For any particular sex the cytoplasmic genes sometimes will be inherited, and sometimes won't be inherited depending on who you mate with, so it's got an inherent vulnerability to cheats—what happens if one mutant set of mitochondria refuses to shut down?" In other words, once you have a system that is not so rigidly fixed as in the two-sex world, then there is a greater risk of an outbreak of the mitochondrial wars that the sexes evolved to prevent.

As luck would have it, a new bit of evidence seems to confirm his view. Last year, molecular biologist Shigeyuki Kawano at Tokyo University reported that he had found a slime mold with mutant mitochondria that refuse to be shut down and instead force the cell to accept mitochondria from both partners. "It's only one observation," says Hurst, "but it seems too much of a coincidence that the first time this sort of event is seen is in a species which has 13 sexes."

If Hurst is right, systems like that of the slime mold may evolve from time to time, but they will always collapse and head back to binary systems. Or, to put it another way for the 4-year-old, the real reason that there are only two sexes is that if there are more, life just gets too complicated.

–Alun Anderson

Additional Readings

L. Hurst and W.D. Hamilton, "Cytoplasmic Fusion and the Nature of the Sexes," *Proceedings of the Royal Society (London)*, Series B **247** 189 (1992).

L. Hurst "Intra-Genomic Conflict as an Evolutionary Force," *Proceedings of the Royal Society (London)*, Series B **248** 135 (1992).