EVOLUTIONARY BIOLOGY

Flies Unmask Evolutionary Warfare Between the Sexes

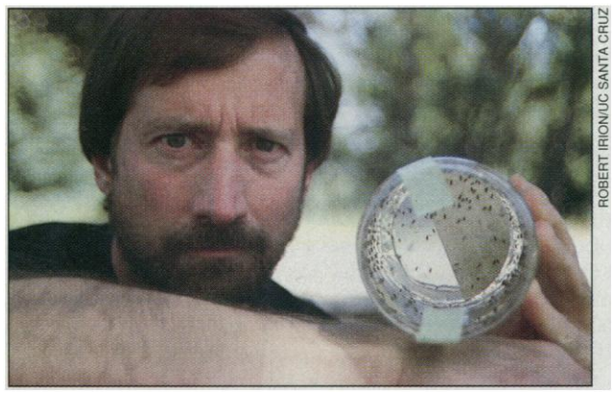
There's yet another front in that most enduring of all wars, the battle between the sexes. Since the 1970s, evolutionary biologists have suspected that males and females are locked in a coevolutionary struggle to achieve reproductive success at their mate's expense, and in many species the female's reproductive tract is thought to be a key battlefield. There, the sexes produce various proteins that affect everything from sperm motility to female sexual desire, apparently in an effort to chemically outgun each other. Now this notion of coevolution between the sexes has been put to the test.

In an ingenious experiment with fruit flies, William R. Rice, an evolutionary biologist at the University of California, Santa Cruz, has decoupled what he terms the sexes' coevolutionary dance, forcing the females to stand still, in evolutionary terms, while the males continued their adaptive moves. And he discovered that the dance is actually more of a duel. In work reported in this week's issue of *Nature*, Rice found that the males rapidly evolved to take advantage of the females. After about 40 generations, the "supermale" flies fathered more offspring, prevented their competitors from siring progeny in their common mates—and caused their female partners to die young.

Rice's study thus provides elegant experimental support for a basic tenet of sociobiology—that the reproductive interests of males and females are essentially at odds, and that this antagonism fuels at least some evolutionary change. "The sexes do coevolve through time, just as do host [organisms] and parasites, or predators and prey," Rice says. "We've always thought that this [coevolution] was going on, but it's been very hard to see," says Dan Howard, an evolutionary biologist at New Mexico State University in Las Cruces. "Rice has finally unmasked the chemical antagonism between the sexes." Howard thinks that Rice has also unmasked a possible consequence of this warfare: It can put up barriers to fertilization, leading to genetic divergence between populations and thus to the formation of new species.

> **"The sexes do coevolve through time, just as do ... predators and prey."**
> **—William R. Rice**

Rice investigated these questions in a species known to wage intersexual chemical combat—the fruit fly *Drosophila melanogaster*. Researchers already knew that the seminal fluid of male fruit flies contains some proteins that are toxic to the females. For example, one male peptide both encourages the female to increase her egg-laying rate and dampens her sexual appetite—chemical tricks that the male may use to ensure that only his sperm fertilize the eggs. Another male protein apparently kills off rivals' sperm and inadvertently poisons females in the process.



ROBERT IRION/UC SANTA CRUZ

Cheek to cheek. Rice found that even as they make love, fruit flies make evolutionary war.

The female, in turn, secretes chemicals in her oviduct that may fend off the male's proteins; other proteins may reduce the number of sperm or switch off the male's sexual suppressant, or both. These countermeasures help turn the female's reproductive tract into a chemical gauntlet for the male's would-be progeny. Many of the 5000 or so sperm that a male may ejaculate into a female simply fall out, or perhaps are weakened by the female's secretions. The female can only store about 500 sperm, which she holds in special internal pockets until her eggs are ready for fertilization.

The reason for this chemical antagonism is that "the interests of males and females are not the same," says Howard. "The male's overriding interest is to fertilize the egg and to do it before a rival male does, while the female's goal is to make sure that the egg is fertilized with only one sperm" in order to avoid developmental problems. The female also seeks to have plenty of sperm available at the right time for egg-laying while receiving as few toxins as possible. "As far as I can tell, all a female [fly] wants is sperm"—sperm without toxins, says Rice. "But what she gets is sperm plus the seminal fluid, which the male may use to control her and to keep out other males, turning her body into a battlefield."

This power struggle has evolutionary consequences, as Rice revealed by permitting only male flies to evolve. He managed this feat in part by taking advantage of a genetic idiosyncrasy of fruit flies: Each offspring receives one set of genes from its father and one from its mother; in male flies, these genes do not recombine. By using specially constructed chromosomes, Rice enabled the paternal set of genes (or the male haplotype) to be transmitted exclusively from father to son. The maternally derived genes (the female haplotype) also passed to sons, but had no effect on the population, because Rice culled all female haplotypes. Thus the males in Rice's experiment were essentially cloned, while the females were merely "egg-laying machines," he says. As a result, the males could follow their own evolutionary path, separate from the females.

Rice then mated each generation of cloned males with females from a large stock population, in which normal mating presumably kept the sexes in an evolutionary steady state. With no opportunity to adapt to the experimental males, the females were evolutionarily "stuck." But the male clones continued to adapt to the target females, as mutations beneficial to male reproductive success were passed from father to son.

Rice found that those genetic advantages accumulated quickly, and in only 41 generations the males achieved stunning reproductive success. Like stars in a fruit fly version of a bad B movie, these supermales persuaded the females to mate with them more often than with their rivals (possibly via sheer persistence or seductive pheromones), and they fathered a disproportionate number of offspring. But the males' success brought no corresponding increase in the females' fecundity. In fact, females who mated with these Don Juan flies died young, apparently because of the potent load of toxins in the males' seminal fluids, says Rice. "There was no benefit to the females at all from mating with these guys. It was deleterious to them." Even females who mated only once with the supermales died prematurely.

The experiment reveals that under normal circumstances, there is "perpetual coevolution of males and females," says Rice.

For every move by the male to increase his success at the expense of the female, she would normally make a countermove. But when the females' countermoves were blocked, the males' interest prevailed. The findings complement long-standing evidence for behavioral warfare between the sexes, such as forced copulations in ducks and deceitful matings in some primates, notes John Alcock, a behavioral ecologist at Arizona State University in Tempe: "This study demonstrates the level of chemical warfare that exists as well."

The quick genetic response of the evolving males to the sitting-duck females also "shows the speed with which males can exploit females for their own reproductive advantage," says Alcock. And Howard suggests that the speedy evolutionary change means that "barriers to fertilization [between species] can also arise quickly. In fact, you can see such a barrier in its initial stages right there in Rice's experiment." Because the supermales fertilized most of the eggs, normal males were effectively shut out and no longer contributed their genes to the population. When genes don't move freely between groups, the populations are considered reproductively isolated—and thus separate species. Indeed, the reproductive tract right after insemination may be the setting where barriers to gene flow first arise, say Howard, Rice, and many other researchers in evolutionary biology and genetics. "Intersexual competition can thus be seen as a major engine of speciation," says Rice.

But although Rice's demonstration of the evolutionary duel between the sexes wins plaudits all around, not everyone agrees that this intersexual warfare is driving speciation. For example, Chung-I Wu, an evolutionary geneticist at the University of Chicago, puts his money on male-male competition as having a bigger role in speciation, because male reproductive traits evolve faster. "The genetic blueprint for males to make sperm changes at a much more dramatic rate than do equivalent genes in females. It's 10 times faster," he notes. Counters Rice, "Even if sexual coevolution only contributes 10% to the process, that's still significant."

To show that the female's response is also an important factor in driving evolutionary change, Rice may have to reverse his experiment, and hold the males in check and let the females evolve. Sexual conflict theory more or less predicts that the females will turn into the equivalent of fruit fly Ice Queens, mating with only one or two males to limit the amount of toxins they receive and to get "just enough sperm to get the job done," Rice speculates. Will the male partners of such superfemales also meet an early death? Stay tuned: The battle of the sexes is far from over.

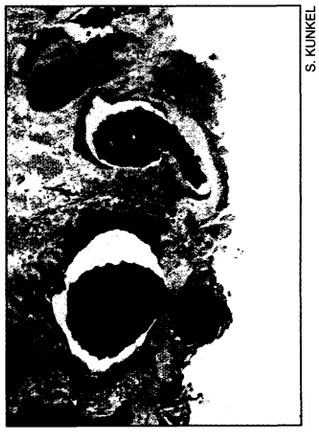
–Virginia Morell

IMMUNOLOGY

Chemokines Take Center Stage in Inflammatory Ills

As any actor knows, becoming a star often requires more than just good looks and talent. Being "discovered" can also take a lucky break. That's true even for biomedicine's stars, such as proteins that may hold the key to new therapies. Take the chemokines, a family of proteins that act as magnets for white blood cells and thus play a key role in eliciting inflammatory responses.

Although immunologists discovered the first chemokine nearly a decade ago, the proteins did not take center stage until late last year when Robert Gallo's group at the National Cancer Institute (NCI) found that certain chemokines suppress production of the AIDS virus, raising the possibility that they might be used to treat the immunodeficiency disease (*Science*, 15 December 1995, p. 1811). "Before chemokines were associated with AIDS, the field was restricted to a small group of investigators doing a very good job of investigating [the proteins]," says Anthony Fauci, chief of the National Institute of Allergy and Infectious Diseases (NIAID). "Now, all of a sudden, everybody is talking about chemokines." They are finding a lot to talk about.



S. KUNKEL

Tight squeeze. Neutrophils leave a blood vessel, presumably in response to a chemokine.

Work reported just last week, for example, suggests an explanation for how the chemokines inhibit AIDS virus reproduction: They may bind to and block a cell-surface protein that the virus must latch onto in order to get into cells (*Science*, 10 May, pp. 809 and 872). But the proteins usually play a different, more widespread role in the body.

Chemokines belong to a large class of intracellular messengers called cytokines that carry regulatory signals from cell to cell. But unlike some better known cytokines, such as interleukin-1 and -2 (IL-1 and -2), which act early in immune responses and tend to activate many kinds of white blood cells, chemokines come into play later and appear to have a much more specialized role in attracting inflammatory cells to damaged or infected areas. "Chemokines are key to mobilizing [white blood cells] to sites of inflammation," says Joost Oppenheim, whose team at the NCI co-discovered the first two true chemokine molecules. "They are a fundamental part of the inflammatory host defenses."

That puts them in the frontlines of the body's defenses against a wide variety of invading pathogens in addition to HIV. These include numerous other viruses, bacteria, and parasites such as the malaria-causing *Plasmodium vivax*. Just how chemokines work against these other invaders varies, sometimes dramatically, from pathogen to pathogen, but in general, the chemical messengers pull white blood cells out of the bloodstream, trigger some of them to spew out a potent mix of digestive agents that kill or maim live pathogens, and encourage others to gobble up the remains of tissue damaged by infection or injury. These actions cause the characteristic redness, soreness, and other symptoms of inflammation, which is normally a protective response, causing only limited damage in the interests of clearing up an infection.

But these initially protective chemokine effects can turn into an overzealous attack on healthy tissue, contributing to the damage in a wide range of inflammatory diseases, including short-term conditions like septic shock and persistent disorders such as rheumatoid arthritis. "The response may backfire and cause a lot of symptoms of illness. These are illnesses caused by overenthusiastic inflammatory and immune responses," Oppenheim says.

This dual role of the chemokines, as both fighters and perpetrators of disease, has caught the eye of the pharmaceutical industry. Dozens of companies, ranging from small biotech firms such as LeukoSite Inc. and Repligen Corp., both located in Cambridge, Massachusetts, to industry giants such as San Francisco–based Genentech, have joined the chemokine hunt in the hopes of finding novel therapeutic drugs.

Although researchers hope that the chemoattractors themselves might be useful in AIDS therapy, most current drug development efforts have been spurred by animal studies indicating that chemokine inhibitors may be useful for blocking the destructive inflammation in pneumonia, asthma, and other lung conditions as well as in arthritis and various cardiovascular diseases. "There is an enormous effort by pharmaceutical companies on this," says Charles Mackay,