

# Endocrine Disrupters Trigger Fertility Problems in Multiple Generations

A fungicide and a pesticide, both already known to be toxic to animals, have revealed a potentially even darker side: On page 1466, researchers report that the two chemicals cause fertility defects in male rats that are passed down to nearly every male in subsequent generations. No other known toxin has been shown to do that, according to the study's authors and other scientists. The startling results seem to support the controversial idea that such hormonelike chemicals, known as endocrine disrupters, could be causing population-wide reproductive problems, such as lowered sperm counts in men. But many scientists caution against drawing conclusions until other labs have confirmed the unexpected findings.

"These are remarkable observations. If they're solid and reproducible, they are going

malities in lab animals. Over the past 15 years, many scientists have come to think that these endocrine disrupters are potentially causing harmful effects, such as cancer and reproductive abnormalities, in humans, too.

It was already known that when pregnant rats are treated with relatively high doses of vinclozolin every day, their male offspring are sterile, Gray notes. But Skinner and his team found that when they injected vinclozolin into the abdomens of pregnant rats during a specific window of pregnancy—8 to 15 days into gestation—they got a different result. Although the offspring's testes appeared normal and the rodents could reproduce, their sperm count dropped 20% compared to control mice, their sperm motility was 25% to 35% lower, and the cells within the testes underwent higher rates of apoptosis—a form of cell death.

apoptosis—a form of cell death.

The researchers then bred these males with females born to other pregnant rats similarly treated with vinclozolin. To their surprise, more than 90% of males born from these matings had very similar reproductive abnormalities, as did similar numbers in the next two generations. To determine if the male rats inherited the defect from their fathers, they bred a

second-generation vinclozolin male—its grandmother had been injected with the fungicide—with a normal female. Their male offspring again had nearly identical sperm and testes defects, whereas a vinclozolin-mother female offspring crossed with a normal male did not. The researchers got similar results when they treated rats with methoxychlor, a pesticide used as a substitute for DDT and whose metabolites include an antiandrogenic compound.

That only male offspring were affected suggested that the two compounds had caused mutations in the male cell's germ line, the cells that give rise to sperm, says Skinner. Radiation can increase the risk of cancer in multiple generations by mutating germ line cells, but it triggers such mutations in a small number of germ line cells, so that only a tiny percentage of offspring are ▶



**Infertile ground.** The fungicide vinclozolin, which is sprayed on vineyards like these, can cause fertility problems in male offspring of exposed rats.

to have a large impact on how we look at these kinds of chemicals," says Earl Gray, a toxicologist with the Environmental Protection Agency (EPA). Biologists are stumped by the apparent mechanism of the chemicals; they may alter how genes are expressed in subsequent generations, but without mutating DNA. "It's provocative. But I don't think we have a clue as to what's really happening," says geneticist Robert Braun of the University of Washington, Seattle.

The work was led by reproductive biologist Michael Skinner of Washington State University, whose lab has been studying vinclozolin, a fungicide used in the wine industry. Vinclozolin blocks cell receptors that are normally activated by the hormone androgen. It is just one of a suite of widely used chemicals, from flame-retardants to ingredients in plastics, that can cause reproductive abnor-

## Northrop Withdraws as Los Alamos Race Opens

In an unexpected twist, there's now one less competitor for the 7-year contract to run Los Alamos National Laboratory in New Mexico. Northrop Grumman surprised insiders by dropping out of the race last week, despite public assurances that it was serious about a bid (*Science*, 27 May, p. 1244). Northrop's decision came a day before the University of California's Board of Regents voted 11-1 to vie for the management contract, which UC has held since 1943. Congress forced the competition for the \$2.2 billion laboratory after persistent management and safety scandals. Although Lockheed Martin and a combined UC-Bechtel team lead the pack, the National Nuclear Security Administration has not said whether other teams are in the hunt.

—ELI KINTISCH

## DOE Pushes for Solar Power

Officials at the Department of Energy (DOE) are testing the waters for what some are calling a "Manhattan Project" for solar energy. Despite decades of progress in solar cells and rising gas prices, electricity produced by the devices still costs up to 10 times as much as that produced by fossil fuels. DOE currently spends \$10 million to \$15 million a year on basic solar energy research, such as efforts to discover novel semiconductors that harvest sunlight more efficiently. If DOE officials get the go-ahead from congressional appropriators, that figure could rise as high as \$50 million a year, according to Mary Gress, who manages DOE's photochemistry and radiation research. Officials will preview an upcoming report on solar research next week at a DOE advisory committee meeting.

—ROBERT F. SERVICE

## A Lease on Life for SREL?

If the House of Representatives has its way, the Savannah River Ecology Laboratory (SREL) will have a bit more time to fight a White House plan to shutter it. Under that proposal, the \$8-million-a-year lab would close on 30 September. Although the measure failed to provide new funds for the lab for 2006, language attached to a House spending bill passed last week would allow the Department of Energy lab to operate until next June using any "available funds." The Senate must now decide whether to appropriate new money for the 54-year-old lab.

—ELI KINTISCH

affected. Moreover, the effect gets smaller with each generation. In contrast, the vinclozolin-induced fertility changes occurred in almost every male rat descended from a treated mother. To Skinner and his colleagues, that suggested an epigenetic mechanism might explain their data.

Although they don't mutate the DNA sequence of an animal, epigenetic changes can be inherited and affect how genes are expressed. One common epigenetic change is the attachment of methyl groups to DNA,

which can shut a gene off or turn it on. Indeed, Skinner's group showed that methylation patterns in the testes of affected rats differed from those in control rats. However, they didn't rule out mutation of the animal's DNA sequence, notes epigeneticist Emma Whitelaw of the University of Sydney, Australia. The changes in methylation might simply correlate with the declining fertility, she says: "I'm not sure it's an epigenetic mark."

"We're mostly describing a new phenomenon," acknowledges Skinner. But he is wor-

ried nonetheless. "The hazards of environmental toxins are much more pronounced than we realized," he asserts.

Still, according to EPA, the doses used in the experiment were much higher than the exposure levels allowed for people, and Gray says this single study won't change regulations for vinclozolin and similar antiandrogens. For now, "it's going to be very important for other people to look at this," he says. Adds Braun, "It baffles me."

—JOCELYN KAISER

## GENETICS

# Spliced Gene Determines Objects of Flies' Desire

The male fruit fly is a winged Casanova. He pursues lady flies with a repertoire of song, dance, and well-placed licks that many find impossible to resist. Now, by creating genetically engineered female flies that mimic the male courtship display, researchers have taken important steps toward understanding the biological basis of this complex, instinctive behavior.

In a pair of papers in the 3 June issue of *Cell*, Barry Dickson and colleagues at the Institute of Molecular Biotechnology in Vienna, Austria, report that a gene called *fruitless* (*fru*) sets up the fly brain to produce male courtship behavior in *Drosophila melanogaster*. Female flies altered to use the *fru* gene to make proteins normally made only by males woo other females much as males do. Additional experiments by Dickson's team identify a circuit of neurons in the fly brain that appears to mediate such courtship behavior and sexual orientation.

"I think it's quite remarkable," says Catherine Dulac, a neuroscientist at Harvard University. The work convincingly demonstrates that a single gene can regulate a complex sequence of behaviors, she notes. The team's "very elegant experiments" represent "a start toward understanding how an innate behavior is laid down in a nervous system," says Edward Kravitz, a Harvard neuroethologist.

In the 1960s, scientists discovered that male flies with a mutated *fru* gene become sexually indiscriminate—courting males as well as females. Then, in the mid-1990s, two teams reported that the *fru* gene operates differently in males and females; the cells of each sex read the gene in distinct ways, splicing together different mRNA transcripts. In males, these transcripts produce up to three distinct proteins, whereas the female mRNAs seem to lead to none. The DNA sequence of *fru* suggests that it encodes proteins that regulate the expression of other genes—but no

one knows what those genes might be.

Scientists have hypothesized that male *fru* proteins are necessary and sufficient for male courting behavior, but Dickson's paper is the first to show that directly, says Daisuke Yamamoto of Tohoku University in Sendai, Japan, who led one of the teams that discovered the splicing difference.

The key was making very minor modifications to the region of *fru* that is spliced differently in males and females,

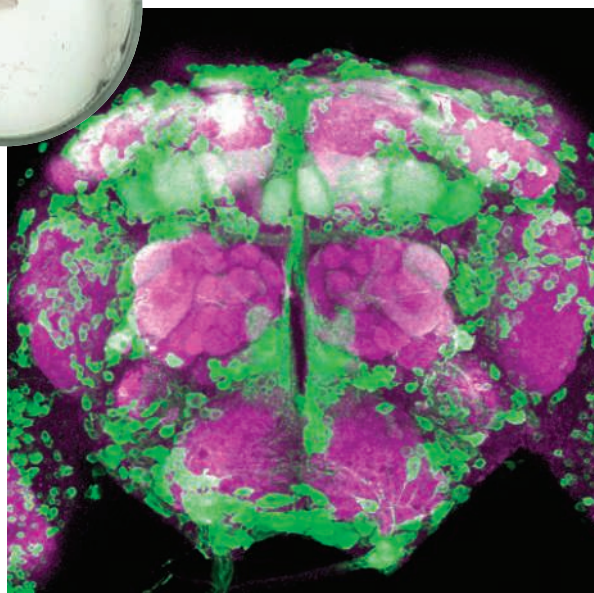
"behavioral switch genes" like *fru* provide a way to hard-wire adaptive behaviors into the brain so that an animal can perform them instinctively. Still, he and others caution against extrapolating the results to sexual behavior in humans. "Clearly, we are vastly more complicated creatures than flies, and our common experience tells us that our sexual interests are not irreversibly set by our genes," Dickson says.

To investigate how *fru* programs the courtship routine into the fly brain, Dick-

son's team engineered additional fly strains. In one, a genetic marker identified all of the neurons in male flies that normally express the male-specific mRNAs of *fru*. Many of the labeled neurons appeared to form a circuit. Key elements of this circuit are olfactory neurons that may be specialized for pheromone detection. Inactivating these cells abolished courtship behavior in male flies, Dickson's team found. Somewhat puzzlingly, the researchers also found a similar circuit of neurons in female flies. This suggests to Dickson that courtship behavior depends not on anatomical differences between the male and female brain but rather on how this circuit functions.

Kravitz suspects that *fru* may also be involved in other instinctive behaviors that differ between the sexes—a possibility he will be investigating with a visiting postdoc from the Dickson lab. "We're pretty sure these same genes are involved in whether flies fight like males or females," he says. If so, *fru* may turn out to make male fruit flies fighters as well as lovers.

—GREG MILLER



**Going courtin'.** Spliced the right way, *fru* establishes a "courtship" circuit of neurons (green) in the male fly brain and makes females court other females (*inset*).

forcing female flies, for example, to splice the gene as males normally do. Although the sexual anatomy of these females appeared to be entirely normal, their behavior was dramatically altered. They courted other female flies, using all steps of the male courtship ritual, short of attempting copulation. Yet, male flies altered to splice *fru* as females do barely courted at all. Dickson hypothesizes that