Battle of the Sexes

Mouse studies shed light on whether maternal and paternal genes wage war

By JOHN TRAVIS

Even if your mother and father had the best of marriages, they likely argued at times over how to raise you. It's natural for parents to disagree about what's best for their kids. What is surprising, however, is that this parental conflict may have existed on a genetic level even before your birth. Moreover, while you were in her womb, your mom—and SCIENCE NEWS sincerely hopes this doesn't make you regret sending that Mother's Day card last week—may not have been concerned only about you but also about herself and the children she might have after you.

Such startling conclusions emerge from the struggle to explain the genetic oddity known as imprinting, in which the parental origin of a gene determines whether or not it functions (SN: 5/20/89, p. 312). Although imprinting affects relatively few genes, it flies in the face of the laws of Mendelian inheritance, which hold that a child inherits two active copies of a gene, one from each parent.

"Having two copies of each gene is to a large extent a good backup," notes Laurence D. Hurst of the University of Bath in England.

Imprinting, however, silences one of the parental copies of a few important genes. As a result, the only working copy of an imprinted gene comes from either the father or the mother. This, it seems, would tend to make an organism more vulnerable. "Now, you just need one mutation and you're a goner," says Hurst.

Imprinting therefore offers a formidable challenge for evolutionary biologists such as Hurst. They must account for the shedding of this genetic safety net. "Here, we have something that is slapping us in the face and saying, 'Come and explain me!'" says Hurst. "We need a compelling reason for imprinting."

For the past decade, the most compelling hypothesis has been that moms and dads have conflicting interests when it comes to passing on their genes. Simply stated, a dad cares only that offspring carry on his genes, but a pregnant mother must balance the needs of her current baby against her drive to have additional progeny. This disparity, according to the theory, eventually leads to paternal genes that encourage embryos to grow large by drawing additional resources from the mother and maternal genes that seek to limit such growth.

Three new studies have recently put the parental-conflict model of imprinting to the test. The theory, despite some blows, remains standing. "By and large, it's a convincing hypothesis," says Wolf Reik, who studies imprinting at the Babraham Institute in Cambridge, England.

Most mammals play the field. In other words, both males and females mate with multiple partners throughout life. This promiscuous lifestyle, known as polyandry, is central to the parental-conflict theory of imprinting.

From the male perspective, a father has no interest, genetically speaking, in progeny resulting from a female's unions with other males. His sole concern is that the offspring that share his genes survive and thrive. As a result, the theory holds, evolution will select for paternal genes that help embryos become as big as possible, even if that growth threatens the mother's health.

On the other hand, a female mammal mates with many partners in order to broaden the genetic diversity of her offspring and thus increase the odds that her genes will continue on. She wants to take care of any current embryos but not at the expense of her future reproductive success. Consequently, the conflict model predicts that females would evolve genes that counteract the paternal genome's efforts to enlarge an embryo.

The theory of a genetic battle of the sexes among mammals was first laid out a decade ago by David Haig of Harvard University and Tom Moore of the Babraham Institute. Scientists have since tallied more than two dozen imprinted genes in mammals. Many of them indeed regulate the growth of embryos and do so in a manner consistent with the conflict hypothesis. Some of the paternally active genes, for example, encourage growth of the placenta, the tissue through which an embryo draws nutrients from the mother.

The classic imprinting example that supports the conflict model describes the gene for insulinlike growth factor-2 (Igf2) and the gene for a protein that binds to the growth factor and leads to

its degradation (Igf2-r). The gene for Igf2 is imprinted: The mother's copy is inactive in an embryo, but the father's copy takes charge. This agrees with the model since Igf2 promotes embryonic growth; embryos lacking the paternally active copy of the gene end up smaller than normal.

In contrast, only the maternal copy of the gene for Igf2-r is active, which fits in with its apparent duty of limiting growth. When the maternal copy is disabled by mutation, embryos develop into larger-than-normal offspring.

Imprinted genes with no obvious impact on an embryo's growth don't discourage supporters of the conflict model. Such genes may have been accidentally affected when a nearby gene that does regulate growth was imprinted, notes Shirley M. Tilghman of the Howard Hughes Medical Institute at Princeton University.

If imprinting results from infidelity, what about a monogamous species? Since its male and female genes are not at war, the conflict theory predicts that such a species wouldn't have needed to imprint genes or, as the species becomes monogamous, it might erase any imprinting.

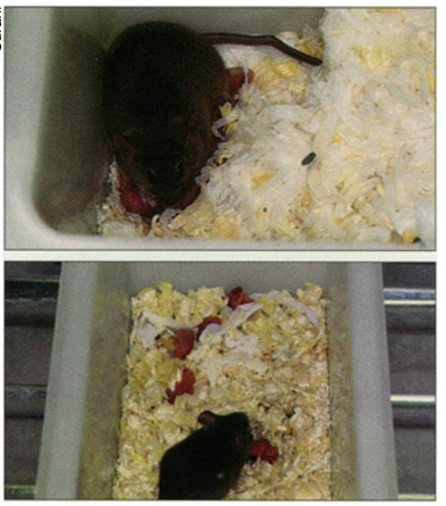
Single-minded devotion among mammals is rare, however. Tilghman and her colleagues recently stumbled upon a publication from the 1960s that described cross-breeding between a monogamous mouse species and a closely related polyandrous one. Provocatively, when mothers came from the promiscuous species and fathers from the monogamous one, the pups were much smaller than normal. In the reverse case, the embryos grew so abnormally large that they rarely survived and the mothers even had difficulty giving birth.

One explanation of these results is that the monogamous mice had no imprinting. For example, the paternally active Igf2 gene from males of the polyandrous species would then be paired with an unsilenced copy of the Igf2 gene from a female of the monogamous species. The result: increased embryonic growth.

Intrigued, Tilghman and her colleagues obtained mice of the same species, repeated the cross-breeding, and saw the same results. For example, a polyandrous father and monogamous mother produced embryos with placenta up to six times the size of the placenta from the opposite mating, the group reports in the December 1998 NATURE GENETICS.

Yet when the researchers actually examined whether the monogamous rodents had genes silenced by imprinting, they got a surprise. "Both the polygamous and monogamous mice were imprinting the same genes," says Tilghman. In other words, monogamy had not caused a loss of imprinting, as the conflict model would apparently suggest it should.

Surani



Mother mice normally closely tend their pups (top). However, a mother harboring an inactive working copy of an imprinted gene ignores her young, neither retrieving nor feeding them (bottom).

Observing a loss of imprinting would have been strong confirmation of the conflict model, says researchers, but its continued presence in a monogamous species doesn't deal a death blow to the theory for several reasons. First, the species' switch to a largely monogamous mating system may have been too recent for imprinting to disappear. Second, it's not clear how faithful the mice actually are. Although the rodents seem to pair-bond for life, a female will take a new partner if the male dies, for example, notes Tilghman.

"I wasn't surprised when imprinting turned up in the so-called monogamous mouse. Even though it's a lot more monogamous than [other mouse species], there is still substantial partner change," says Haig. "It's more than sufficient to explain the maintenance of imprinting."

How then do the scientists explain the altered embryonic growth observed in progeny of cross-bred mice? The hybrid offspring experience dramatic disruptions in their normal patterns of imprinting, which likely explain the size abnormalities, says Tilghman. For example, maternal copies of some imprinted genes that are normally silent become activated in the hybrids.

Tilghman speculates that incompatible imprinting may keep groups of similar animals reproductively separated and thus encourage speciation. She and her colleagues plan to survey other animals, such as marsupials and certain fish, to continue testing the monogamy issue.

The parental-conflict model argues that imprinting may develop in genes participating in embryonic growth, but what about genes that govern adult behavior? That's the provocative question raised by recent studies of mice with mutations in imprinted genes called *Mest* and *Peg3*. Mothers with mutations in either of these genes give less than stellar

care to their newborn offspring.

The mutant animals, described in the April 9 SCIENCE and October 1998 NATURE GENETICS, were created by M. Azim Surani of the University of Cambridge in England and his colleagues. The team first made mice lacking *Mest*, a gene whose paternal—but not maternal—copy is normally active throughout the growing embryo, notably in the developing brain. The gene also functions in many tissues of adult mice, again including the brain.

The researchers found that mice lacking their working paternal copy of *Mest* developed normally—except that they were significantly smaller than usual. This growth retardation, a finding that supports the parental-conflict model, did not seem to disturb the general health of the rodents.

The scientists had begun breeding the small mutant mice when they realized that the females were neglecting their pups. In laboratory tests, the mothers built nests poorly and didn't retrieve displaced pups as readily as normal mice did.

This aberrant maternal behavior was evident even immediately after birth. "When pups are born, one of the functions the mother performs is to chew off and clean up the umbilical cord and remove the placenta. The *Mest* [mutant] mice showed deficiency in this behavior," says Samuel A. Aparicio, one of Surani's coworkers.

Similar results emerged when Surani and his colleagues mutated the paternal copy of *Peg3*, which is also active in the embryonic and adult brain of mice. The mutant mice were smaller than normal but otherwise healthy. When the mutant females gave birth, however, they neglected their pups so much that few survived. Compared with normal mothers, the mutant females took 8 times longer to build nests and 11 times longer to retrieve wayward pups.

The scientists also discovered that the females carrying *Peg3* mutations failed to provide milk to their young, even though their mammary glands were full. Further studies revealed a possible explanation. In the brain region called the hypothalamus, cells that secrete a chemical called oxytocin play a crucial role in females' ability to lactate. Normal females have nearly 4,500 such cells, but the female mice lacking *Peg3* have, on average, less than 3,000 of them.

At first glance, it's striking that two paternal genes somehow encourage a mother's care of her young. "Maternal behavior is obviously [something] that could have important consequences for the survival of genes," notes Aparicio.

It is far from clear, however, that the conflict model of imprinting can accommodate these findings. Why would females have inactivated a gene, such as *Mest* or *Peg3*, that would promote their daughters' caring for offspring?

While he is playing with ideas about how adult behavior might lead to imprinting, Haig stresses that the parental-conflict model doesn't have to account for the role of *Mest* and *Peg3* in maternal behavior. That influence may have evolved after the genes had already become imprinted. "The simplest thing to say is that the genes are imprinted because of their effects on fetal growth," says Haig.

Although Hurst considers that type of explanation perfectly legitimate, it illustrates why he's a bit frustrated with the parental-conflict hypothesis. Like many theories in evolutionary biology, it's almost impossible to prove or disprove.

"There doesn't seem to be a test that we can do to show that the theory is actually wrong," laments Hurst. That said, the evolutionary biologist admits that he still favors, albeit reluctantly, the parental-conflict model.

Hurst sums up his current take on the conflict theory of imprinting by paraphrasing Winston Churchill's oft-quoted judgment of democracy. "It's the worst of all explanations, except for all the others," he says. □

Chemistry

From Seattle at a meeting of the Electrochemical Society

Catalysts make hydrogen under the hood

Government researchers have discovered a new class of catalysts that convert fossil fuels into clean-burning hydrogen gas at temperatures much lower than previously thought possible.

Because combustion of hydrogen produces only heat and water, automakers hope to tap it as fuel for a new generation of pollution-free vehicles. Without a national system of hydrogen filling stations, however, engineers are designing cars with onboard reactors that can generate hydrogen from gasoline (SN: 11/1/97, p. 279). Currently available reactors operate at temperatures of 1,100°C or higher, says Shabbir Ahmed of the Department of Energy's Argonne (Ill.) National Laboratory. These hot temperatures mean high engine wear and energy usage.

The new catalysts, whose composition the Argonne researchers have not revealed, operate below 800°C and work on a variety of fuels. Gasoline and diesel exposed to the materials yield a mixture of gases that is 60 percent hydrogen, while natural gas yields 42 percent. The catalysts also seem not to plug up reactors with solid carbon, a problem with other catalysts.

About 2 liters of a catalyst in pellet form can generate a hydrogen flow that will yield about 3 kilowatts of power. A light vehicle needs 40 to 50 kW to run. If others confirm the results, says Argonne's Michael Krumpelt, "industry will have to come to its own conclusions" about the usefulness of the catalysts. The scientists are currently seeking a patent for the materials. —*C.W.*

Can graphite nanofibers store hydrogen?

Tiny graphite fibers can hold more than 40 percent of their weight in hydrogen, says Nelly M. Rodriguez of Northeastern University in Boston. Such fibers, only about 20 nanometers in diameter, could be a compact, lightweight way to store hydrogen as fuel in portable devices (SN: 1/16/99, p. 47).

At the molecular level, the fibers consist of graphite disks stacked like dinner plates and connected at their edges by oxygens. The hydrogen diffuses into the space between the plates, which accommodate a large volume of gas, says Rodriguez.

Other researchers have doubts. "It's physically unrealistic," says Michael J. Heben of the National Renewable Energy Laboratory in Golden, Colo. "The conceptual limit is one hydrogen per carbon atom, which is 8 percent by weight." —*C.W.*

Electricity switches a mirror to a window

Thin films of a gadolinium-magnesium alloy possess a curious property: When hydrogen diffuses into the material, the shiny, reflective metal turns as clear as a piece of glass (SN: 3/23/96, p. 182). The alloy is a natural choice for privacy windows, optical shutters, and active displays, but pumping gas into and out of a chamber isn't a practical switching method.

Researchers at Philips Research Laboratories in Eindhoven, the Netherlands, have made a prototype device that changes the alloy from a mirror to a window simply with application of an electric voltage. A thin layer of liquid potassium hydroxide covering the alloy sends hydrogen to the metal and takes it back in response to changes in voltage.

This design lasts through only 500 switching cycles, though, says Philips' Anna-Maria Janner. A protective layer of palladium peels off the alloy, allowing a hydroxide to form. The hydroxide slows the switching time so much that the material no longer turns completely transparent. Janner and her colleagues are now trying to replace the potassium hydroxide with organic materials that won't have this problem.

One possibility is a polymer called imidazole. If the polymer remains stable through many switching cycles, "we will think of making a gel out of it," Janner says. The researchers would then have the basis for a completely solid-state device. —*C.W.*