of axis rotation and extending from the top to the bottom of the container. The extended vortex can be spotted with magnetic resonance imaging, says Zurek, enabling the group to "pull out vortex lines and count them one by one." The Helsinki group went on to measure vortex formation at varying temperatures and pressures, and the results, says Kibble, "seem to fit [Zurek's predictions] very well."

Lacking such sophisticated imaging apparatus, the Grenoble researchers cool their superfluid liquid helium-3 to 130 microkelvin, a temperature five times lower than the Helsinki group reached and a world record. That's cold enough to stabilize the vortices formed in the liquid helium, enabling the Grenoble group to measure their density by determining how much energy they absorb from the surrounding superfluid. The researchers know exactly how much energy the neutron deposited in the helium-3—"a very well-known 764 kiloelectron volts [KeV]," says Godfrin—and they can measure the energy of the system before and after the entry of the neutron. Inevitably the difference comes to less than 764 KeV. The missing energy has no place to go but into the formation of vortex lines. "We don't actually see any vortices," says Pickett. "All we do is infer they're there from the energy deficit. But if we agree they're there, we can work out how far apart they are, and the distances agree very well with this scenario of cosmic-string formation."

The two experiments lend considerable credence to the idea that topological defects formed in the early universe. But the next step in cosmologists' postulated chain of events—the idea that cosmic strings provided the "seeds" for galaxy formation—is less amenable to a test. "The experiments allow us to estimate the initial number of defects that might have formed in the early universe," says Kibble, but then cosmologists have to follow the strings through a few billion years of cosmic evolution to see if they end up with the right properties to seed galaxy formation. "That's a long chain of reasoning," he says, "and the experiments in helium-3 don't help us with that." But at least they strengthen the first step in this cosmic chain.

–Gary Taubes

BEHAVIORAL GENETICS

Does Nature Drive Nurture?

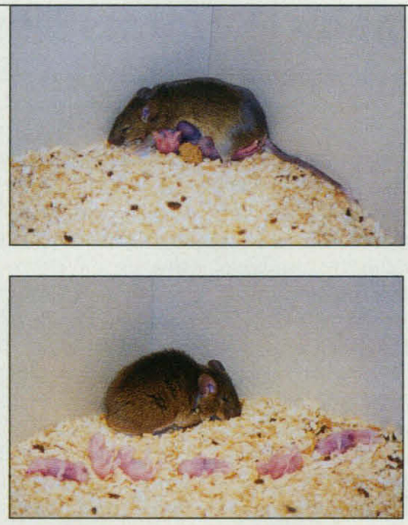
Researchers who create "knockout" mice by inactivating specific genes in the animals sometimes get less than they bargained for. The mice show fewer abnormalities than expected, or even none at all. But sometimes the researchers get much more. Take the knockout mice created by Jennifer Brown.

When Brown first bred the mice, in which she had inactivated a gene called *fosB* that is known to play a critical role in controlling the expression of other genes, she noticed something odd: Most of the pups were born healthy, but quickly died. "Only one or two [of a handful of mothers] had surviving pups. It was enough to pique my interest and provoke me to do a larger experiment, but not enough to make me think there was that much going on," recalls Brown, an M.D.–Ph.D. student who works in the lab of neuroscientist Michael Greenberg at Harvard Medical School.

A few months later, in the spring of 1995, she knew that her first impression was wrong. Something important was going on. By this time, two dozen pairs of parents with the *fosB* knockout had had litters. Again, most of the pups died. "Even the people in the animal facility were asking me what was happening with these mice," says Brown.

As Brown, Greenberg, and co-workers report in the 26 July issue of *Cell*, what appears to be happening is that *fosB* heavily influences—if not downright controls—whether a mother mouse nurtures her offspring. "This is among the first bit of evidence that nurturing in mammals has a genetic component," says Greenberg, who has long studied the relationship between the *fos* family of genes (there are four in all) and neurons.

The study, which merges molecular genetics and behavioral science, is winning plaudits from researchers in both fields. "I think it's a lovely piece of work, and it really shows the power of molecular genetics to analyze interesting behavioral problems," says Eric Kandel of Columbia University, who works in both areas. As Brown and Greenberg are the first to acknowledge, however, they haven't completely ruled out the possibility that the altered behavior of the mother knockout mice is caused by a physiologic or anatomical defect resulting from the *fosB* deletion, rather than from altered neuronal responses. "We need to do more work to really resolve whether this involves direct action of *fosB* in neurons," says Greenberg.



BROWN *ET AL.*, *CELL*, VOL. 86 NO. 2, JULY 26, 1996

Mother inferior. A normal mouse mother *(top)* cares for her pups, while a *fosB* knockout *(below)* ignores hers.

Still, the link between *fosB* and behavior does not come as a complete surprise. During the past few years, many molecular geneticists have shown that the *fos* gene family is one of several turned on in neurons shortly after an animal receives some kind of environmental stimulus, such as contact with a pup. The proteins produced by these so-called "immediate early genes," in turn, kick other genes into action, leading ultimately to a neuronal response to the stimulus. And among the brain areas where *fos* family members are active are ones that other researchers have shown to be necessary for normal nurturing behavior.

Still, given the uncertainties of working with knockouts, Brown began the current work not knowing what she would find—if anything. But when she noticed how poorly the knockout mothers cared for their pups, ignoring them until they died, the team began an extensive study to see how *fosB* inactivation might be causing the problem.

The researchers ran several tests to make sure that the knockout mothers really were poor nurturers. For example, they removed pups from their mothers for an hour, put three back, and timed how long it took the mothers to move them to the nest. Wild-type mothers retrieved their first pup within 20 seconds and all three within 4 minutes. In contrast, only one of 10 knockout mothers retrieved all her pups within the 20-minute observation period, and the rest took more than 16 minutes to retrieve their first pup.

But the failure of the pups to survive may have had less to do with this behavior than with possible non-neuronal problems—if, for example, loss of *fosB* made it impossible for the knockout mothers to produce milk. Their mammary glands showed no abnormalities, however. The researchers next examined levels of hormones, such as progesterone and oxytocin, that are known to affect nurturing behavior. Again, wild-type and mutant mothers showed no differences. A check of several brain regions showed no obvious physical abnormalities in the knockouts, either.

Nor did the mutants appear to have olfactory abnormalities that might prevent them from recognizing their young through smell. Using an "aversive conditioning paradigm," the researchers showed that the mutants had

no problems learning to avoid a distinctive odor. They caution, however, that these results don't rule out a more subtle defect, such as one that would lead the mice to respond to an odor improperly.

The only difference the Greenberg team could detect between the knockouts and normal mice was in the preoptic area (POA) of the hypothalamus. As behavioral neuroscientist Michael Numan and colleagues at Boston College have shown by causing lesions in rat brains, the POA plays a central role in regulating nurturing behavior. And Greenberg and Brown found that when they exposed normal female mice to pups, production of the FosB protein was turned on in the POA. That, of course, couldn't happen in the knockouts, which lacked a functional *fosB* gene. This finding, they conclude, suggests that FosB may induce nurturing behavior by acting specifically within POA neurons.

Tom Curran, a *fos* gene expert at St. Jude Children's Research Hospital in Memphis, Tennessee, says these results mesh well with molecular genetics studies that link *fos* to the brain. The new data, Curran says, "would fit very nicely with something we'd like to believe." Yet he notes that the current work does not rule out the possibility of the *fosB* deletion affecting nurturing behavior indirectly by affecting, say, a mother mouse's sense of smell. If so, he says, "that would still be interesting, but it wouldn't be as interesting as saying the gene *fosB* is responsible."

Other researchers, such as behavioral endocrinologist Robert Bridges of Tufts University School of Veterinary Medicine, are skeptical about the notion that one gene controls one behavior, even in mice. "A tremendous number of interactions regulate gene interactions," says Bridges, who nevertheless stresses that he was much impressed with the work.

Given the many remaining caveats about *fosB*'s role in mice, Greenberg and others are even more circumspect about whether the findings can be extrapolated to other species, particularly humans. When asked about that, all Greenberg would say was: "There is a *fosB* gene in humans. From there it's up to your imagination."

–Jon Cohen

CANCER RESEARCH

Ancient Remedy Performs New Tricks

Ten years ago, researchers in Shanghai found that all-*trans*-retinoic acid (ATRA), an off-the-shelf treatment for skin cancer, was a potent drug against acute promyelocytic leukemia (APL), a rare blood cancer that up to then had been uniformly fatal (*Science*, 17 November 1995, p. 1144). Now, working with a group from Harbin, China, the scientists have identified what might be an even more effective APL treatment. The new drug is a modification of a traditional remedy for a variety of ailments, and researchers have used the latest lab techniques to uncover a possible explanation for the power of this ancient remedy.

In work conducted over the past 20 years, the Harbin team found that an arsenic compound in a traditional Chinese medicine appeared to achieve a complete remission, for varying lengths of time, in more than 70% of APL patients. Some have remained disease-free after 20 years. New laboratory results by both groups, which appear in the August issue of the journal *Blood*, indicate that the compound works by inducing the cancer cells to go into apoptosis (programmed cell death), a finding that puts the traditional remedy squarely in the mainstream of modern chemotherapy research.

Western cancer experts are intrigued by these findings. "They purified a substance that was part of a broth that had been used for centuries, and then they went out and did the trials," says oncologist Stephen Friend of the University of Washington, Seattle, who describes the results of those trials as "striking." Other scientists familiar with the work are sufficiently impressed to say that more studies are warranted. "I like the mechanism, but the next step is to find out how active it may be in patients," says Samuel Waxman of Mount Sinai Medical Center in New York. "In any case, the story of how we got to this point is fascinating."

The story that Waxman is referring to began 25 years ago in far northeast China, when Zhang Ting-Dong and a team of doctors from Harbin Medical University were sent out to the countryside during the Cultural Revolution to document Mao Tse-Tung's belief in the superiority of traditional Chinese medicine over Western practices. Zhang discovered that the secret ingredient in a remedy for arthritis, skin disorders, and other maladies is arsenic trioxide. Although the treatment occasionally produces serious side effects, including liver damage and even malignancies, when given orally, Zhang found that its toxic effects could be greatly reduced by administering it intravenously in lower doses. He tested the drug's efficacy against a number of cancers and found it especially potent against APL; almost half the patients in one trial, for example, were disease-free 5 years later.

"It's another surprising finding from the same group that surprised everybody with ATRA."
—Raymond Warrell

Zhang's findings were published in 1992 in a Chinese journal. Two years later, molecular biologist Chen Zhu and colleagues at the Shanghai Second Medical University picked up on the work in an attempt to help 15 terminal APL patients, some of whom had suffered second and third relapses after treatments with other chemotherapeutic drugs, including ATRA. Working with the Harbin group, the Shanghai team achieved complete remissions in 14 of the 15 patients treated with arsenic trioxide. The side effects, such as nausea, were relatively minor. Although three of the patients have since died, several have enjoyed remissions lasting for 18 months or more, much longer than those produced by ATRA, whose clinical effectiveness had been discovered by Chen's mentor, hematologist Wang Zhenyi. "The survival rates are much higher than would be expected with ATRA," says Raymond Warrell of the Memorial Sloan Kettering Cancer Center in New York, who has helped to establish ATRA as the current standard treatment. "Clearly they need to look at more patients, over a longer time, but it's definitely another surprising finding from the same group that surprised everybody with ATRA."

Arsenic trioxide appears to work by a mechanism much different from that of ATRA. Rather than killing APL cells, the all-*trans*-retinoic acid causes them to differentiate and stop dividing uncontrollably. In contrast, the work reported in the *Blood* paper shows that arsenic trioxide triggers cell death in an APL cell line. The precise mechanism is still very much in question, says Friend, although the paper hints that the compound hinders the activity of an oncogene that blocks apoptosis when it is activated in tumor cells.

Despite the promising clinical and lab findings, Waxman cautions that the arsenic trioxide does not eliminate all the leukemic cells in the patients, which may leave them vulnerable to later flare-ups of the cancer. Still, he plans to collaborate with the Shanghai group to find the best treatment protocols for APL and explore whether the drug is effective against other tumors.

For his part, Wang plans to continue merging the latest molecular techniques with traditional Chinese medicine. "I've heard of other compounds that are effective in inducing differentiation and apoptosis," he says. "We hope to learn more about them."

–Jeffrey Mervis