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