Silver-spoon genes found for queen bees

For the first time, scientists have identified some of the genes that switch on during the mysterious process that can turn genetically identical honeybees into either queens or commoners.

Just 48 hours after hatching, future queens and workers differ in the activity of seven genes, report Jay D. Evans of the Department of Agriculture's Bee Research Laboratory in Beltsville, Md., and Diana E. Wheeler of the University of Arizona in Tucson. In the May 11 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, they describe five genes more active in workers and two genes more active in royalty.

"People think of the worker as a cutdown version of the queen," Wheeler says. "Maybe the queen is just a cutdown version of a worker."

At first, a honeybee can be whatever her sisters want her to be. For 24 hours, all hatchlings dine on royal jelly that nursemaids regurgitate. The milky slurry contains nectar, pollen, and bee secretions.

After that period, the bees that tend the youngsters sometimes single out a few for royal treatment, enlarging their cells and continuing to feed them royal jelly. These larvae grow into large adults with functional sex organs.

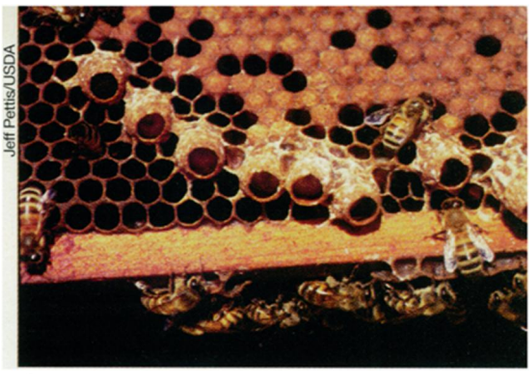
The nursemaids, however, leave most larvae in small cells and feed them worker jelly, a formula of nectar, pollen, and different secretions. By 48 hours after hatching, a larva can no longer switch to the royal fast track. Instead, she grows up with withered ovaries but greater visual acuity and more capacity for learning.

Earlier research showed that nursery differences affect gene activity, but scientists couldn't identify the specific genes. After Russian scientists in 1996 described an analytical technique called suppressive subtraction, "we pounced on a way that finally worked," Evans relates. He and Wheeler are the first to apply the method to honeybees.

The researchers started with larvae just 48 hours after they hatched. From future workers, Evans collected messenger RNA, molecules produced by active genes to instruct the protein-making machinery. From that RNA, he made complementary single strands of DNA.

To find worker genes, he added an identifying snippet of DNA to these DNA strands. He then flooded pools of the tagged strands with single strands of DNA made from queen messenger RNA.

At this genetic sock hop, strands from genes active only in the workers failed to find a partner from genes active in the queen. Genes that were much more active in workers than in queens left some wallflower strands, too. After several such mixings, Evans sequenced the tagged leftovers. He then repeated the process but tagged queen instead of worker DNA. Finally, he looked for resemblances between the bee genes identified and known genetic sequences.



Jeff Pettis/USDA

Big cells hold hatchlings on the royalty track, which includes special food.

A bee gene active in only worker larvae resembles the DNA for a fatty acid–binding protein. This strikes H. Frederik Nijhout of Duke University in Durham, N.C., as the most exciting find. He speculates that it might bind to the much-studied juvenile hormone considered key in controlling the queen-worker split.

"What the hormone is doing we have no idea," Nijhout says. Evans and Wheeler's work "gives us hope that we'll in fact find the answer, and it gives us the technique with which to do it." —*S. Milius*

Therapy pits useful gene against tumor

In about half of lung cancer cases, a gene called *p53* has mutated and thus fails to encode a protein that oversees programmed cell death. In the absence of this protein, which helps curb the growth of damaged or abnormal cells, cancer can gain a foothold. Replacing such defective *p53* genes with fresh ones has shown promise against a variety of cancers in animal experiments and studies of a few patients (SN: 8/31/96, p. 134).

Scientists now report further progress in such localized gene therapy. By enlisting a virus to deliver *p53* to tumor sites in 28 people with lung cancer, they temporarily stabilized or reversed the course of the cancer in more than half the patients. The findings appear in the May 5 JOURNAL OF THE NATIONAL CANCER INSTITUTE.

The patients, average age 65, had lung cancer that was either inoperable or was no longer responding to radiation treatment or chemotherapy. The researchers injected the tumors with an adenovirus engineered to contain *p53* genes. The virus was also modified to prevent it from replicating and thus causing the upper respiratory infection that it might otherwise bring about.

During the 6-month treatment period, patients received one to six monthly injections of the modified virus. The researchers delivered a range of doses—from 1 million to 100 billion viral units—to gauge any toxicity of the treatment.

Three of the 28 patients died of cancer before doctors could make a 1-month follow-up examination. Among the 25 others, tumors shrank in 2 patients, stabilized in 16, and continued to grow in the other 7.

The dose of virus mattered. Cancer progressed unabated in three of five patients who received injections of 10 million or fewer viral units. In contrast, only 4 of 20 patients getting a larger dose experienced cancer growth.

Biopsies of patients' tumors revealed that the injected *p53* was active. The rate of programmed cell death, or apoptosis, had at least doubled in response to the gene therapy, adds study coauthor Jack A. Roth, a surgeon at the University of Texas M.D. Anderson Cancer Center in Houston.

One 72-year-old woman made a striking, although brief, turnaround. After radiation therapy had failed to knock out her cancer in 1994, doctors tried chemotherapy in 1996, also to no avail. She received six large doses of *p53,* the last in June 1997, which shrank her tumor by more than half. A checkup in March 1998 showed no active cancer, but she has since died.

A 70-year-old woman previously treated with drugs, radiation, and lasers—to clear a tumor that was blocking one bronchial tube—also responded well to the gene therapy. The injections cleared the tube and restored air flow. However, after the *p53* treatments ended, her cancer returned and she died.

Only one patient survives from the group, a person in whom the *p53* treatment had stabilized the cancer.

Lung cancer patients with inoperable, untreatable tumors typically have less than a 10 percent chance of living a year.

The study shows that *p53* is "a viable target" for a genetic approach to cancer treatment, says Nick R. Lemoine, a molecular oncologist at Hammersmith Hospital in London.

The scientists "should be congratulated on their efforts," says Ralph R. Weichselbaum, a radiation oncologist at the University of Chicago. However, he adds, "this gene therapy would probably work better with radiation or chemotherapy. I'm a little skeptical that it's going to work as a strategy by itself."

Roth agrees. "It's been the history of oncology that you see some of the greatest effects with combined-modality treatments," he says. —*N. Seppa*