

GENOMICS

Puzzling Decline of U.S. Bees Linked to Virus From Australia

Researchers have found an imported virus that may be associated with the sudden disappearance of honey bees in the United States, known as colony collapse disorder (CCD). This baffling syndrome, which earlier this year made headlines around the world, may have afflicted as many as 23% of beekeepers in the United States and caused losses of up to 90% of hives in some apiaries. The identification of a suspect is an important step, says Nicholas Calderone of Cornell University. "Before, we didn't even have circumstantial evidence."

The suspect is a pathogen called Israel acute paralysis virus (IAPV). A team of researchers reports online in *Science* this week (www.sciencemag.org/cgi/content/abstract/1146498) that they found the virus in most of the affected colonies they tested, but in almost no healthy ones. If the virus proves to be the cause of CCD, it could have international economic implications, for the researchers point to Australia as a possible source. Since 2005, U.S. beekeepers, especially those struggling to keep up with the insatiable demand for almond pollination in California, have imported several million dollars' worth of bees from Australia. The researchers report that they have found IAPV in imported Australian bees.

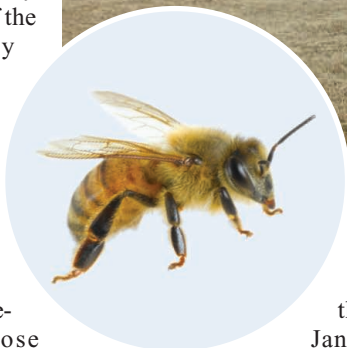
The investigation is still in an early stage, and there are skeptics. Another group has not found any link between IAPV and CCD. "This paper only adds further to the confusion surrounding CCD," argues Denis Anderson, an entomologist with the Australian Commonwealth Scientific and Industrial Research

Organisation (CSIRO) in Canberra, who has not participated in either group.

The abrupt loss of bee colonies in the United States, first reported last fall, has been a big mystery. Although some scientists aren't convinced that the phenomenon—based largely on anecdotal reports from beekeepers—is really any different from past declines in bee populations



Hazardous import? The sudden loss of honey bees, particularly among trucked hives, has been linked to a virus that may have arrived with bees from Australia.



(*Science*, 18 May, p. 970), bee researchers from around the country met in Florida in January and formed a working group to track down the culprit. The co-chairs, entomologists Diana Cox-Foster of Pennsylvania State University in State College and Jeffery Pettis of the U.S. Department of Agriculture's Bee Research Laboratory in Beltsville, Maryland, acquired samples from collapsed colonies and asked molecular biologist W. Ian Lipkin of Columbia University's Mailman School of Public Health to help in the search for pathogens.

Lipkin initially pooled samples from four beekeeping operations that had been struck with CCD and, for comparison, he

lumped together samples from two operations that had remained healthy. When the group ran the samples through a gene sequencer, they found an array of microorganisms. All the bees had a rogue's gallery of pathogens, but the samples from the CCD operations tended to be more disease-ridden, with two viruses and two microsporidian parasites especially prevalent.

Next, the team went back and analyzed samples from individual hives. IAPV turned up in 25 of the 30 sick colonies but in just one of the 21 healthy colonies. "It's a good marker," says Mady Hornig of Columbia University. Others note, however, that bees in hives suffering from CCD tend to accumulate all sorts of secondary diseases, so IAPV infection could be a consequence rather than a cause of the disorder. "It's a chicken-and-egg problem," says bee virologist Joachim de Miranda of the Sveriges Lantbruksuniversitet in Uppsala, Sweden.

Jerry Bromenshenk of Bee Alert Technology in Missoula, Montana, doubts the link to CCD. His collaborators at the U.S. Army's Edgewood Chemical Biological Center in Maryland have spotted more than a dozen known and new viruses, including IAPV, in bees from Florida, California, and Australia, but none is associated with CCD. "We've got lots of pathogens but no clear pattern yet," Bromenshenk says.

Evidence in the paper points to Australia as the source of IAPV. All of the operations infected with IAPV had either imported bees from Australia or stored their hives close to other operations with Australian bees. None of the CCD-free beekeepers, located in Hawaii and Pennsylvania, had Australian bees. Moreover, the team ordered bees from Australia and discovered IAPV in most of them. Samples of bees collected in Pennsylvania and Louisiana in 2004—before the importation of bees began—turned out negative.

But some researchers point out that this limited testing doesn't rule out the



possibility that IAPV may have already been in the country before U.S. beekeepers began importing Australian bees. And Anderson notes that IAPV does not seem to be causing harm in Australia.

Ilan Sela, a plant virologist at the Hebrew University of Jerusalem who first isolated IAPV in 2002 from dead bees taken from Israeli colonies, says IAPV is far from harmless. In experiments reported in the 5 June issue of *Virology*, Sela and colleagues show that, when injected, IAPV causes paralysis and death in 98% of bees within days. If fed to the bees, they survive just a few days longer. "IAPV kills," he says.

So why is there no CCD in Australia,

even though IAPV is presumably there? One reason could be that, unlike the United States, Australia remains free of the varroa mite, which spreads pathogens and weakens the immune system of bees. But that can't be the whole story, Pettis notes, because CCD also appears to be absent in Canada and Israel, where varroa mites are a problem and beekeepers have imported Australian bees for years.

Pettis says other stresses in the United States such as poor nutrition and long-distance trucking may make IAPV lethal. Within the next few weeks, the team will begin a complicated set of experiments intended to test whether IAPV can cause

CCD either by itself or in combination with three other pathogens and stresses. In the meantime, Cox-Foster says, beekeepers should keep their bees as healthy as possible and not reuse hives from collapsed colonies.

If IAPV does turn out to be a cause of CCD, there is encouraging news from Israel. Sela has found that some bees can resist the virus. About a third of bees sampled in Israel have incorporated the virus into their genome. In his experiment, almost 20% of these bees survived when injected with IAPV. Sela says that raises the possibility of breeding IAPV-resistant bees.

—ERIK STOKSTAD

BIOMEDICINE

HIV Drug Shows Promise as Potential Cancer Treatment

What comes around goes around: The first AIDS drug to come to market was initially developed to treat cancer, and now a drug approved for AIDS is being tested in humans as an anticancer agent.

A team led by medical oncologist Phillip Dennis at the U.S. National Cancer Institute (NCI) in Bethesda, Maryland, found evidence that drugs currently used to inhibit HIV's protease enzyme might also work against cancer. In the 1 September 2007 issue of *Clinical Cancer Research*, Dennis and colleagues describe test tube and mouse experiments indicating that three of these drugs show activity against six different types of cancer. One, nelfinavir, proved better than the others, leading Dennis to launch a clinical trial. "The amazing thing is we moved from preclinical to clinical studies in one-and-a-half years," says Dennis. Typically, pharmaceutical companies spend 5 to 10 years testing a promising compound before moving into human trials, notes Dennis, but "repositioning" an already-approved drug takes advantage of the already abundant data on toxicity and dosage.

It was two toxic effects of protease inhibitors in HIV-infected people that led Dennis to the idea that they might work against many cancers. Dennis's lab specializes in studying a cell-signaling pathway, Akt, that's activated in many cancers.

It's well established that inhibiting the Akt pathway can lead to a buildup of lipids and glucose. "We hypothesized that if we could identify drugs that elicited those toxicities, we would find a good Akt inhibitor," says Dennis. This led them to HIV protease inhibitors, which can cause patients to develop characteristic lipid deposits and hyperglycemia.

As Dennis and co-workers describe in *Clinical Cancer Research*, it turns out that Akt inhibition only explains part of nelfinavir's anticancer effects. "We don't think Akt inhibition is the crucial mechanism," says Dennis. Instead, they found that nelfinavir induces stress of the endoplasmic reticulum, which in turn leads cells to self-destruct through mechanisms known as autophagy and apoptosis. "The mechanism part of this paper is quite striking," says oncologist Samuel Broder, chief

medical officer at Celera Genomics in Rockville, Maryland. "This is very, very interesting."

Broder, former director of NCI, in the 1980s helped discover the first anti-HIV drug to come to market, AZT, which at the time was an abandoned anticancer agent.

Dennis hopes to enroll 45 patients, all of whom have solid tumors that do not respond to treatment. Dennis initially wants to determine whether cancer patients

can tolerate nelfinavir at higher doses than used to treat HIV. "The maximum tolerated dose and toxicities of nelfinavir have never been established in humans," he says. Although this could trigger the hyperlipidemia and hyperglycemia often seen in HIV-infected patients taking protease inhibitors, Dennis notes that these are controllable conditions, and, relatively speaking, not a major concern of people who have an otherwise untreatable cancer. "If we're not causing profound bone-marrow suppression and life-threatening infections, we're pretty happy," he says.

—JON COHEN



Problem/solution? AIDS drugs that caused this man's unusual fat accumulation may have revealed a new cancer agent.