

INFECTIOUS DISEASE

Old Drugs Losing Effectiveness Against Flu; Could Statins Fill Gap?

ST. JULIAN'S, MALTA—With the threat of a deadly pandemic looming large, flu drugs are coming under increased scrutiny. At a meeting here last week* researchers reported disheartening data showing that the most aggressive of the circulating human flu strains has become resistant to an older class of flu drugs, rendering the drugs all but useless in the yearly battle against seasonal flu and deflating hopes they might be used to fight a pandemic.

But help might come from an unexpected source, according to another study: the cholesterol-lowering drugs called statins. Very preliminary data suggest that these

* The Second European Influenza Conference, 11–14 September.



Over the counter. Tens of millions of courses of Gan Kang, a product containing amantadine, were reportedly sold in China last year.

drugs, cheap and widely available, might help prevent serious complications from a flu infection. If that's true, statins would offer a glimmer of hope for countries that, unlike the

United States (see ScienceScope, p. 1977) and other wealthy nations, can't afford pandemic vaccines or oseltamivir, the pricey drug of choice for pandemic stockpiles.

Researchers had long known that amantadine and rimantadine, drugs that block a viral protein called M2, easily trigger resistance in the flu virus and that resistant strains can spread from person to person. But even after decades of use, resistance rates were low, says Rick Bright of the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia—until recently. Bright set out to determine when and where the upward trend started, screening more than 7500 flu samples, collected all over the world since 1995, for mutations that confer resistance against both drugs. ▶

PLANT SCIENCE

New Gene Boosts Plant's Defenses Against Pests

With a little help from friends, crop plants may one day be better able to deter herbivores. By tweaking a cellular pathway for producing organic compounds, researchers have, in a proof-of-principle experiment, endowed *Arabidopsis thaliana* with the power to recruit mites as allies against leaf-munching enemies. The insertion of a strawberry gene into the mustard plant leads to two new compounds that attract predatory mites that devour herbivorous spider mites, Iris Kappers, a plant biochemist at Wageningen University in the Netherlands, and her colleagues report on page 2070. "They show it is possible to manipulate the movements of biological control agents through genetic engineering of plants," says Merijn Kant, a plant physiology at the University of Amsterdam.

Through a series of reactions involving multiple enzymes, plants make terpenoids, complex organic compounds that are important to development and growth, as well as to plant-animal interactions, such as pollination and pest deterrence. About 15 years ago, chemical ecologists discovered that lima beans, when infested with spider mites, emit at least one terpenoid that draws spider-mite predators to the scene; strawberries and other plants turned out to use the same defense. Since then, several groups have tried in vain to provide *Arabidopsis* with this capability by adding genes for the various enzymes necessary to make a particular attractant. "It's [been] notoriously difficult," says

John Pickett, a biological chemist at Rothamsted Research in Harpenden, United Kingdom.

Whereas the earlier experiments put enzymes into the plant cell's cytoplasm, Kappers and colleagues at Plant Research International in Wageningen targeted the one they had chosen—a sesquiterpene synthase from strawberries—into the cell's mitochondria, which contain farnesyl diphosphate, a key building block for one mite attractant. The researchers attached an extra piece of DNA, one encoding a peptide subunit that directs a protein to mitochondria, to the enzyme's gene. This was "very clever targeting," says Ted Turlings, a chemical ecologist at the University of Neuchâtel, Switzerland.

In contrast to the lackluster performance of similar synthases active in the cytoplasm, the mitochondrial-located

enzyme exceeded expectations, producing about 25 times more of the expected attractant than had other transgenic *Arabidopsis* plants, the group reports. To their surprise, the researchers found that a second predatory mite attractant, one derived from the first by the removal of four carbon atoms and one alcohol subunit, had also accumulated in their transgenic plants—and sometimes in greater quantities than the intended one.

Kappers and her colleagues tested the effectiveness of the organic compounds by releasing predatory mites into the center of a circle of *Arabidopsis* potted plants that alternated between wild and transgenic varieties. In the experiment, 388 predatory mites headed for the transgenic plants and 197 headed for the wild-type plants. "This is the first study" to show that the strawberry synthase gene can produce effective attractants in other plants, says Turlings.

Still, Ian Baldwin, a chemical ecologist at the Max Planck Institute for Chemical Ecology in Jena, Germany, is concerned that because such plants would continuously emit attractants, predatory mites won't know when and where prey are available. That uncertainty could cause the plant-mite relationship to break down over time, Kappers agrees. So she's looking for the genes responsible for producing mite attractants only after herbivores attack. Nevertheless, says Kant, the new study "is a major step forward in our ability to manipulate this phenomenon ultimately to our own benefit." —ELIZABETH PENNISI



Help on the way. Transgenic *Arabidopsis* can now recruit predatory mites to cut down spider mite (*inset*) infestations.

For H3N2, the most virulent of the three strains that return each winter, a dramatic pattern emerged. Until 2002, no country had resistance rates higher than 10%. But in 2003, the rate shot up to 58% in China, then jumped to 74% in 2004. Hong Kong, South Korea, and Singapore followed with similar explosions, and samples taken during the 2005 flu season in Europe and the United States show that resistance has climbed to 14.3% and 11.5%, respectively.

The cause of the upswing is unclear, but Bright says over-the-counter sales of amantadine in China may have played a role. The drug is an ingredient of several anticold and anti-flu cocktails sold in China. The leading product, called Gan Kang, is widely available for about \$1.50, and a recent report in *China Business* put its 2004 sales at \$80 million, or more than 50 million courses. Widespread use may have favored resistant virus strains, says Bright, and the dramatic jump in 2003 may be a result of the SARS panic that year.

Fairly inexpensive, amantadine and rimantadine are primarily used against seasonal flu in the United States and Japan, says Arnold Monto of the University of Michigan, Ann Arbor.

The finding may deal a fatal blow to plans, under way in a few countries, to add amantadine to pandemic stockpiles.

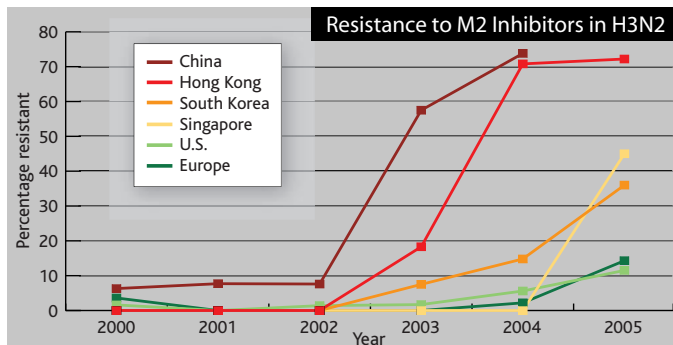
That option had already become less appealing after the discovery that H5N1 avian flu strains isolated in Thailand and Vietnam were resistant to the drug—a finding some have linked to veterinary use of the drug in China (*Science*, 24 June, p. 1849). The finding that a human strain now shows widespread resistance—and the fact that pandemic viruses may arise when avian and human strains swap genes—makes it even less appealing.

Instead, most governments are choosing oseltamivir, a drug that blocks a viral protein called neuraminidase. So far, resistance to that drug is rare, and resistant viruses don't seem to grow as well. Still, the CDC study "shows that we should watch and worry," Monto says.

But many countries have other concerns: They don't have the means to buy large stashes of antiviral drugs or, for that matter, pandemic vaccines. That's where the inexpensive statins might come in. Over the past decade, researchers have discovered that these drugs not only lower cholesterol but also reduce levels of immunomodulators called cytokines, dampening inflammation. This is thought to contribute to their protection

against cardiovascular disease, but it may also explain why in three studies so far, patients on statins appeared to fare better in bacterial infections in which inflammation plays a major role, such as sepsis and pneumonia.

Because flu viruses trigger cytokine release as well, and complications from flu include heart disease and pneumonia, David Fedson, a retired medical director of Aventis, wondered whether statins might be useful in treating flu. At Fedson's urging, clinical epidemiologist Eelko Hak and colleagues at University Medical Center Utrecht in the Netherlands began looking for evidence in a Dutch database of 60,000 primary-care patients. Such data collections are invariably incomplete; whether a patient was tested for flu or bacterial infections often isn't recorded, for instance. Nonetheless, Hak found tantalizing clues. During flu epidemics between 1996 and 2003, patients who had had at least two statin prescriptions over the previous 12 months had a 26% lower risk of



Rising resistance. H3N2 strains around the world are rapidly losing their sensitivity to amantadine and rimantadine, a trend that started in Asia.

pneumonia and other severe respiratory ailments. In non-flu seasons, statins didn't reduce the risk, suggesting that the drugs offer specific protection against flu complications.

That doesn't position statins as the next generation of flu drugs yet. The results will need to be confirmed in other patient populations, Hak says; pharmacoepidemiologist Christoph Meier of the University Hospital in Basel, Switzerland, says he will report results from a similar study shortly. Data from old clinical trials with statins should be reexamined, adds Hak, whose colleagues in Utrecht are also planning in vitro studies to determine how statins might have a protective effect. Clinical studies would have to show whether statins should be taken prophylactically—as millions of people do—or once a person is exposed or infected.

Questions aside, the findings generated interest among meeting participants such as Frederick Hayden, an antiviral expert at the University of Virginia, Charlottesville: "It's definitely something that should be explored."

—MARTIN ENSERINK

With reporting by Gong Yidong in Beijing.

U.S. Tackles Bird Flu

The Bush Administration says it is getting serious about avian influenza. In a 14 September speech to the United Nations, President George W. Bush announced a new International Partnership on Avian and Pandemic Influenza that "requires countries that face an outbreak to immediately share information and provide samples to the World Health Organization [WHO]." The Department of Health and Human Services also promised technical and medical assistance to Southeast Asian nations and has announced a \$100 million purchase of vaccine to combat the H5N1 bird flu virus, the leading pandemic candidate.

"We welcome the U.S. initiative," says Peter Cordingley, a spokesperson for WHO's Regional Office for the Western Pacific. He adds, however, that "the devil will be in the details." A key question is whether China will participate.

—DENNIS NORMILE AND JOCELYN KAISER

Japan and Singapore Link Up

Singapore's Agency for Science, Technology, and Research and Japan's RIKEN research agency agreed last week to exchange scientists, share research materials and information, and promote joint research projects. "[W]e need to expand cooperative efforts and relations with Asian nations," says RIKEN President Ryoji Noyori. Although details are still emerging, neuroscience, cancer drug targets, and environmental pathogens relevant to Asia will be three areas of focus for the partnership.

—DENNIS NORMILE

On Tap: HapMap

The comprehensive catalog of human genetic variation, known as HapMap, will be published on schedule in October, officials announced last week. The \$135 million public-private effort has identified 3.6 million bases across the human genome that vary from population to population and also from individual to individual. According to the National Human Genome Research Institute, the results should save geneticists a bundle by reducing the multimillion-dollar cost of seeking a disease gene about 30-fold. "In some ways, [HapMap] will have a bigger impact than the sequence did," says Jeffrey Murray, a geneticist at the University of Iowa in Iowa City.

—ELIZABETH PENNISI