Emphysema drugs may boost lung damage

Results from a laboratory experiment hint that two drugs commonly used to treat emphysema may actually enhance the progression of this chronic lung disease, which often afflicts cigarette smokers. Scientists caution, however, that the results are based on *in vitro* studies and thus cannot be used at this time to make recommendations for treating people with emphysema.

Emphysema involves chronic irritation of the bronchial tubes and irreversible damage to the tiny air sacs in the lungs where the exchange of oxygen and carbon dioxide takes place. No cure exists, but physicians often prescribe bronchodilator drugs to widen bronchial tubes and ease labored breathing.

At last week's World Conference on Lung Health in Boston, British researcher Robert A. Stockley reported that two of these bronchodilator agents – theophylline and terbutaline – appeared to boost the activity of many white blood cells called neutrophils in a test-tube experiment. Neutrophils normally help fight bacterial infections, but they may do more harm than good when converging on inflamed lungs.

Stockley and David A. Lomas, who collaborated on the study at the Lung Immunobiochemical Research Laboratory in Birmingham, England, suggest these two drugs may increase the number of neutrophils drawn to the lungs, where they can release elastase, an enzyme that can damage the air sacs. Researchers know that lung tissue inflamed by tobacco smoke or other irritants attracts neutrophils circulating in the bloodstream, a process that can lead to emphysema. If the bronchodilators increase the number of neutrophils traveling to the lung, they might actually increase the severity of established lung disease, Stockley and Lomas say.

The researchers obtained blood samples from healthy, nonsmoking volunteers, isolated the neutrophils and bathed some of these cells in either theophylline or terbutaline. On one side of a synthetic membrane they placed the neutrophils; on the other side they placed a protein known to lure neutrophils. Lomas and Stockley discovered that the number of neutrophils traveling through the membrane was 33 percent greater in theophylline-treated cells than in untreated cells, and terbutaline boosted neutrophil migration by 26 percent over untreated cells.

These emphysema drugs "may possibly make the disease worse," comments A. Sonia Buist, a pulmonary researcher at the Oregon Health Sciences University in Portland. However, she emphasizes, drugs that encourage neutrophils to migrate in a test tube will not necessarily cause more neutrophils to cluster in the lung tissue of emphysema patients. Buist is president of the American Thoracic Society in New York City, which cosponsored the meeting with the American Lung Association.

Lomas says his team plans clinical studies to determine whether theophylline and terbutaline indeed boost the numbers of neutrophils in the lung tissue of emphysema patients. In addition, he says, the researchers must determine whether patients who have used these drugs show more severe lung damage than patients who have not.

– K.A. Fackelmann

Caterpillar call-of-the-wild aims at ants

Butterfly caterpillars don't have it easy. Some become victims of parasitic wasps and flies, which inject their eggs into the juicy larvae. These caterpillars suffer slow deaths as wasp hatchlings consume them from the inside out. Others get swept from their leafy perches by low-flying adult wasps in search of fast food.

But many caterpillars in the families Riodinidae and Lycaenidae – which metamorphose into the beautiful, widely distributed butterflies commonly called "metalmarks" and "blues" – don't have these problems. They live in relative comfort by surrounding themselves with bodyguard ants. They appease the ants by secreting sugary fluids; the ants, in turn, keep predators at bay.

But how do they attract the ants in the first place? It took a dedicated entomologist with a tiny microphone to find out.

Philip J. DeVries of the University of Texas in Austin used a custom-designed recording system to tape the sounds made by riodinid caterpillars of the species *Thisbe irenea*. When he held the microphone against the surface upon which a caterpillar was walking, he detected a simple, repeated vibratory pulse. These were not footsteps, however. The sounds were made by the rapid tapping of tiny body structures, called vibratory papillae, against the surface.

Until now, the purpose of vibratory papillae has remained a mystery, but DeVries finds that the rhythmic drumming of these tiny appendages attracts ants. Indeed, the roughly 16-pulse-per-second, 896-hertz signal closely resembles some vibratory messages that other entomologists have identified as a component of ant communication. DeVries' study points to the intriguing possibility that some insects have evolved calls designed to summon unrelated species into symbiotic relationships.

In laboratory experiments and field studies in Panama, DeVries showed that caterpillars whose papillae he had surgically removed failed to produce calls and were tended by significantly fewer ants. Listening to 13 other riodinid species bearing vibratory papillae, he recorded calls similar to those of *T. irenea*. "Prior to this report, sound production was unknown from butterfly caterpillars, nor was it known from any symbiotic association with ants," DeVries writes in the June 1 SCIENCE.

His recordings of 44 other neotropical caterpillars, none of which associate with ants, revealed no vibratory signals. Interestingly, however, the entomologist did detect vibratory signals from 23 other ant-associated caterpillar species bearing no vibratory papillae. How these species produce calls remains unknown, he says.

"It's a pretty neat paper," says Robert Robbins, an entomologist specializing in caterpillar-ant relations at the National Museum of Natural History in Washington, D.C. He says entomologists have suspected that vibratory papillae may have a signaling role, and that caterpillars actively recruit protective coteries of ants rather than simply waiting for them to arrive. "This puts a lot of random observations into perspective," Robbins says. "And it may open up all kinds of research into kinds of mutualism based on sound communication." *– R. Weiss*

Bits of uncertainty: Quantum security

The trouble with sending a secret message is that the recipient must have a key for deciphering it. This means the two parties must initially either meet in person or risk sending the key by some less secure communications channel, and that invites interception. Inspired by an idea first proposed nearly a decade ago, a group of researchers has now designed and constructed a device that uses the uncertainty principle of quantum physics to provide a safe but public means for transmitting vital, secret information.

The device uses extremely faint flashes of light – only one photon per flash – to carry messages. Each photon has a certain linear polarization (whether the electric field associated with the light is oscillating horizontally or vertically) and a certain circular polarization (whether the electric field is rotating in a right-handed or left-handed sense about its direction of travel). According to the uncertainty principle, there's no way to measure a photon's linear and circular polarizations simultaneously. Measuring one disturbs the other.

A sender can use the polarizations of individual photons to send a sequence of signals to the receiver, randomly choos-

ing whether to encode a bit of information as a specific linear or circular polarization. For each photon detected, the receiver chooses randomly which type of polarization to measure. About half the polarization measurements would match the values the sender transmitted. By ascertaining which photons were correctly measured, the sender and receiver could derive a code, known only to them, which would serve as a key for encrypting and deciphering messages.

Because any measurement attempted by a third party would unpredictably alter a photon's polarization, an eavesdropper couldn't intercept the transmission without irrevocably scrambling the message and alerting both the sender and receiver to the surreptitious surveillance. To check for eavesdropping, the receiver would simply compare notes with the sender, ascertaining what the results for a number of selected measurements should have been. Statistical deviations from the expected results would signal an eavesdropper's presence.

This so-called "quantum public key distribution" system is the first communications system ever built to depend on the uncertainty principle to ensure secrecy, say its inventors, Charles H. Bennett of the IBM Thomas J. Watson Research Center in Yorktown Heights, N.Y., and Gilles Brassard of the University of Montreal. "The system relies on the uncertainty principle to enable its users to detect eavesdropping on the quantum channel, even by an opponent with superior technology, and reject the compromised transmissions."

After playing with the idea for several years, Bennett and a colleague constructed a working model of the system last summer. The device consists of tiny diode lasers for generating faint light flashes and detectors for picking up the signals. The entire apparatus sits within a light-tight box about 13 inches long. A computer program controls the apparatus, tallies the signals sent, received and intercepted, and displays the results.

Because it is relatively slow and can be used only for communicating random bits, the apparatus is best suited for transmitting cryptographic keys. Once the two users establish a key, they can exchange secret messages by way of a faster, conventional communications channel.

However, the device's present size severely limits its usefulness. Bennett, who described his demonstration model at last week's Eurocrypt conference in Aarhus, Denmark, now plans to build an improved device using an optical-fiber cable for transmitting light pulses over distances up to 500 meters. Going to greater lengths is tricky because the light pulses must necessarily be weak, which means they travel only a limited distance along optical fibers before fading away.

– I. Peterson

Organ transplant drug tied to cancer risk

A new study links an anti-rejection drug used in most organ transplants to the development of cancer in heart recipients. The cancer, called non-Hodgkin's lymphoma, appears especially prevalent in patients who received higher-than-average doses of the drug, known as OKT3. But even low doses may carry an added risk of the lymphoma, which can kill the patient within a month or two after an otherwise successful transplant, researchers reported last week.

The study is the first to look for a specific link between OKT3 and non-Hodgkin's lymphoma. Many transplant surgeons express surprise at the new findings, saying their own experience suggests the drug is not especially carcinogenic. But the surgical department at Loyola University Medical Center in Maywood, Ill., where the study was performed, has halted preoperative administration of OKT3, reserving it instead as a last resort for patients who show signs of acute organ rejection.

Surgeons generally administer a combination of immunosuppressive drugs, including OKT3, before transplantation and/or afterward if signs of rejection appear. OKT3 consists of monoclonal antibodies made by cultured mouse cells. It destroys white blood cells that play a crucial role in organ rejection.

When the drug won FDA approval four years ago for use in kidney transplants, it was the first monoclonal antibody licensed for therapeutic use in humans. Today, virtually every U.S. kidney recipient gets it. In addition, surgeons have used OKT3 for years in many heart and liver transplants, all the while gathering added data on its safety and efficacy.

Lode J. Swinnen and his colleagues became suspicious of the drug when several of their heart transplant patients developed non-Hodgkin's lymphoma, a cancer of the lymphoid tissues. Previous studies had shown that severe immunosuppression can trigger lymphoma in a small percentage of cases, but the Loyola team noted a higher incidence that seemed to warrant further analysis.

The researchers reviewed the records of all Loyola heart recipients since 1984. About half of them had received drug combinations that included OKT3 before and/or after surgery; others had received combinations in which a different drug replaced OKT3. Ten of the 154 transplant patients later came down with non-Hodgkin's lymphoma; nine of those were in the OKT3 group. All told, 12 percent of the OKT3 patients developed the lymphoma, compared with 1.5 percent of patients not receiving OKT3.

Moreover, among patients receiving a cumulative OKT3 dose of more than 75 milligrams (a standard course is 70 mg), the percentage getting lymphoma jumped to nearly 36 percent. All of the high-dose patients who got lymphoma died of the disease within one to two months, despite aggressive anticancer therapy. Those who developed lymphoma after lower doses had less severe cases that typically arose four to 18 months after their transplants.

Statistical analysis of all known lymphoma risk factors in the heart recipients – including use and dose of other immunosuppressive drugs – indicates that OKT3 was "the only one that significantly correlated" with cancer appearance, Swinnen said at the annual meeting of the American Society of Clinical Oncology in Washington, D.C.

The implications for people who receive the drug for kidney transplants are not immediately clear, Swinnen and others say. Most kidney recipients get 5 mg per day for 10 to 14 days, for a total dose of up to 70 mg, according to Richard Salem, a spokesman for Ortho Pharmaceutical Co. in Raritan, N.J., which manufactures the drug. The company "is aware of and is analyzing the [new] data," Salem told SCIENCE NEWS.

Swinnen says doses higher than 70 mg generally accumulate in people receiving both a prophylactic course of the drug and additional doses following signs of rejection. The value of preventive immunosuppression for organ recipients remains controversial, he says.

Mitchell L. Henry, a transplant surgeon at Ohio State University in Columbus who has studied OKT3, says prophylactic use of the drug is "fairly common" in kidney, heart and liver transplants, but that cumulative doses above 75 mg "are probably unusual." Nonetheless, Swinnen notes, four of the group's 10 lymphoma cases occurred in patients who received only a single course of the drug. While stressing that the statistical correlation does not by itself prove OKT3 causes lymphoma, he adds: "We're worried enough to stop using it [prophylactically]."

FDA spokeswoman Faye Peterson says OKT3's approval in 1986 included a special provision that Ortho continue to gather data on the drug's safety. In particular, she says, FDA wanted to watch for drug-associated lymphoma. Peterson says Ortho has forwarded some data to the agency for review.

Surgeons at several major transplant centers told SCIENCE NEWS they have noticed no particular link between lymphoma and OKT3. Swinnen responds that no other study has specifically looked for the link. "I'd be surprised if other centers do not report this later," he adds.

Swinnen calls for a reassessment of the drug as a preventive treatment, while recommending that physicians follow OKT3 recipients closely for early signs of lymphoma.

– R. Weiss