Study links acid reflux, esophageal cancer

The human esophagus gets its share of irritation. Stomach acid bubbling up into this tube often inflames it, resulting in the misnamed but familiar problem of heartburn. An acid-blocking pill or antacid usually seems to take care of the difficulty.

Researchers, however, have asked whether such chronic inflammation can lead to more serious trouble. Prolonged irritation has been shown to disrupt cell growth. For example, steady inflammation of the liver from hepatitis has been linked to liver cancer. New data suggest a similar risk for the esophagus.

Heartburn, or acid reflux, is more common in patients diagnosed with a cancer called adenocarcinoma of the esophagus than it is in healthy people, Swedish researchers report in the March 18 NEW ENGLAND JOURNAL OF MEDICINE. While the study doesn't prove that acid reflux causes cancer, chronic irritation presents "one potential mechanism" for it, says study coauthor Jesper Lagergren, a gastrointestinal surgeon and epidemiologist at the Karolinska Institute in Stockholm.

Esophageal adenocarcinoma is quite rare. Seeking a link with heartburn, Lagergren and his colleagues compared 820 healthy people with 189 patients who had recently been diagnosed with this cancer. The participants had an average age of almost 70.

The researchers found that 60 percent of the cancer patients had had acid reflux at least once a week for 5 years or more, compared with only 16 percent of the control group. While 3 percent of the controls reported acid reflux more than 3 times a week, 22 percent of the cancer patients did. Likewise, 3 percent of the controls reported reflux going back more than 20 years, compared with 21 percent of the cancer patients.

"This is one of those studies that confirms what everyone believes," says David Y. Graham, a gastroenterologist at Baylor College of Medicine and the Veterans Affairs Medical Center, both in Houston.

Researchers haven't ascertained how the cancer develops. The link connecting heartburn and cancer may be a syndrome called Barrett's esophagus, a precancerous condition in which the lining of the lower esophagus is replaced by cells that resemble stomach-lining cells, says Graham.

Previous studies indicated that about 10 percent of heartburn sufferers have Barrett's esophagus. Although only about 1 percent of people with Barrett's esophagus develop esophageal cancer in any given year, it's still considered a risk factor. Most people with esophageal adenocarcinoma have had Barrett's esophagus.

In the Swedish study, 62 percent of the patients with esophageal adenocarcinoma had signs of Barrett's. The actual correlation may be much higher because by the time cancer is diagnosed, tumors may have overtaken and obscured the Barrett's lesions, says Henry P. Parkman of Temple University School of Medicine in Philadelphia.

The new study indicates that people seeking treatment for chronic heartburn might benefit from being tested for Barrett's esophagus, Parkman adds, so that those who have the condition could be screened for adenocarcinoma. —*N. Seppa*

Amoeba betrayed by anticannibal defense

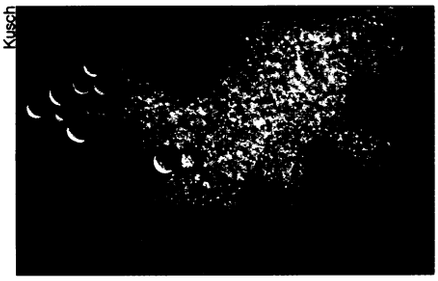
Although substantially smaller than *Tyrannosaurus rex, Amoeba proteus* terrorizes the cell-eat-cell jungle of a drop of pond water. That dangerous predator, however, shows one weakness in its hunting performance. Some of its prey detect a chemical that the amoeba releases and thrash backwards out of range. In a rare insight into predation, scientists may have figured out why the hunter keeps giving itself away.

The amoeba's one-celled snacks, members of the genus *Euplotes*, are just a few of the many organisms that mount a defense on demand—such as fleeing or growing spines or thickening a shell after picking up a chemical cue. These so-called inducible defenses raise a difficult question. What evolutionary benefit could possibly accrue to the predator?

For amoebas, the answer lies in a vital function of the telltale chemical, proposes Jürgen Kusch of the University of Kaiserslautern in Germany. In the March ECOLOGY, he presents data indicating that the peptide, called A-factor, prevents cannibalism by clone mates.

Some theorists have speculated that evolution would have removed tattle-tale chemicals unless some great benefit to the predator constrained that tendency. Researcher Drew Harvell of Cornell University, coeditor of *The Ecology and Evolution of Inducible Defenses* (1999, Princeton), comments, "This is the first experimental study that I know of that suggests a real constraint."

Kusch tested his idea by feeding beads to



Amoeba proteus *gulps beads, about 30 micrometers in diameter, in a test of what might be an anticannibal defense.*

amoebas. They readily engulfed plain beads or ones coated with albumin. However, amoebas ate few beads treated with A-factor and rejected them entirely when concentrations of the peptide became too high.

It could be a self-recognition cue, Kusch says. Amoebas multiply by splitting—no one has observed sex—so clone mates with the same A-factor accumulate.

"It makes no sense to multiply and afterwards to eat each other," Kusch says. "It's a waste of time and of energy."

Harvell says she wants to see more evidence before accepting self-recognition as A-factor's main function.

Kusch's proposal is "really an interesting idea," says Stanley Dodson of the University of Wisconsin-Madison. He notes that some theorists have taken a different tack, suggesting that predators benefit from revealing themselves and thus avoiding wiping out their food supply in a single feast. "That's never been demonstrated," he says. —*S. Milius*

Pumping electrons: Look Ma! No heat!

Heat buildup has always plagued electric circuits. As electronic components continue to shrink, even small amounts of heat become troublesome. Now, scientists have developed a way of pumping electrons through tiny circuits that may eliminate the dissipation of energy as damaging heat.

"This is a new means of making charge move," says Charles M. Marcus of Stanford University, who led the research. To make their pump, he and his team have used an existing method of making a device known as a quantum dot (SN: 4/11/98, p. 236). The dot confines electrons to a region within a thin layer of a semiconductor or metal.

To move electrons through their pump, the scientists manipulate the wave properties of electrons within the dot. By exploiting those properties, the researchers control current completely via the principles of quantum mechanics—the physics of the smallest bits of matter.

"I think this experiment is very significant," comments Qian Niu of the University of Texas at Austin. "It is really the first experiment that demonstrates that you can use a pure quantum effect to pump electrons." He and David J. Thouless of the University of Washington in Seattle formulated theories in the 1980s and early 1990s that indicated the feasibility of such quantum pumping.

In previous experiments, scientists have created electron pumps from quan-

tum dots or other electron-confining structures. However, they have always relied to some extent on a classical-physics effect, the mutual electrostatic repulsion of electrons, to control flows in and out of the device. Pumps employing that effect can give electrons extra energy, causing undesired heating.

The new pump works by varying the probability that an electron is present at any particular location, Marcus explains. A fluctuating pattern of probabilities arises from interference between electron waves.

Marcus and his colleagues at Stanford and the University of California, Santa Barbara fabricated their micrometer-square dot in a sandwich of gallium arsenide and aluminum gallium arsenide. They describe the device, which operates at a frosty 330 millikelvins, in the March 19 SCIENCE.

Electrodes plated on the top and bottom surfaces of the semiconductor structure allow the researchers to apply voltages. Some act as confining walls to electrons. Other oscillating signals, intentionally out of sync with each other, drive the pump. When they are on, "it's as if the walls start to shake," Marcus says.

The shuddering of the walls shifts the pattern of probabilities that an electron is in a given location, making it possible for electrons to enter the dot from outside and for others to be ejected.

The research team does not make direct heat measurements on the new device but draws on other experimental indications, as well as theory, to argue that heating is minimal. "Inside the device, it's reasonable to assume there is a dissipationless current flowing," Marcus says. *—P. Weiss*

Microscopic vessels merge to mix molecules

A new technique that blends minuscule amounts of chemicals can help researchers study the biochemical reactions that occur inside cells.

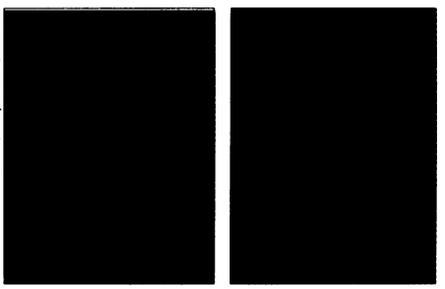
Richard N. Zare of Stanford University and his colleagues encapsulate solutions in tiny spheres, or vesicles, less than 5 micrometers in diameter. By fusing the vesicles, the researchers allow the solutions to combine and react.

Clyde F. Wilson of Stanford described the new technique last week at the Pittsburgh Conference in Orlando, Fla. The Stanford researchers and their collaborators from Göteborg University in Sweden and Pomona College in Claremont, Calif., also report their results in the March 19 SCIENCE.

"This technique comes closer to mimicking what goes on in cells as opposed to in free solution," says Zare. In a cell, molecules repeatedly bump into the cell membrane, which affects the reaction rate. "These [vesicles] are the tiniest test tubes you've ever heard of," he says. Each can hold as little as a billionth of a trillionth of a liter (10^{-21} l).

The researchers make the microscopic containers out of phospholipids, long molecules that assemble into a double-layer membrane. With a laser beam or a thin glass tube, Zare and his colleagues trap the vesicles and move them around. If they bring a pair close together and then zap them with several electric pulses, the two vesicles unite into one.

To demonstrate this fusion, the researchers made containers containing green and red fluorescent dyes and joined



D.T. Chiu, *et al.*/SCIENCE

Two vesicles, about 5 micrometers in diameter, contain green and red fluorescent dyes (left). After a series of electric pulses, the vesicles fuse together, and the blended dyes appear orange (right).

them. The contents mixed together, and the resulting single sphere glowed bright orange. They also combined calcium ions in one vesicle with an organic compound in another.

"I think the work is truly amazing," says Zeev Rosenzweig, a chemist at the University of New Orleans. In a standard test tube, what limits the reaction rate is how fast the molecules can drift toward each other, he notes. In vesicles, however, the reactants don't have far to travel, so other factors influence the rate.

Rosenzweig thinks that this technique could eventually be used to study reactions between individual molecules. "Try to take two molecules and react them in a beaker, and they will never make it," he says. In the microscopic test tube, however, one single molecule would have no problem meeting another. *—C. Wu*

Drug blockades blood vessels' energy

Last year, a media frenzy over a new class of drugs raised hopes of a cure for cancer. Researchers have now discovered how one of these drugs may work. This knowledge could guide the development of smaller, more easily produced agents to eradicate tumors.

Angiostatin, one of the promising anticancer drugs, starves mouse tumors by blocking the growth of blood vessels that sustain them (SN: 5/2/98, p. 286). Scientists didn't know the cellular mechanism underlying the drug's action. The new discovery suggests that angiostatin deprives blood vessel cells of the energy that they need to proliferate.

Angiostatin sticks to and gums up an enzyme on the cells that line blood vessels, researchers from Duke University Medical Center in Durham, N.C., and their collaborators report in the March 16 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES. This enzyme produces adenosine triphosphate (ATP), the compound that cells break down to obtain energy.

Until now, the enzyme, called ATP synthase, had been found only in mitochondria, the energy-generating capsules that reside within cells. The scientists double- and triple-checked their results to make sure that the enzyme indeed coated the blood vessel cells, which they had extracted from human umbilical cord blood.

"I'd wager no one would have guessed that," says Duke biochemist Gordon G. Hammes, who studied the enzyme when it was first examined 30 years ago.

Although surprising, the finding "fits what's going on in the tumor microenvironment," says the study's lead author, Tammy L. Moser from Duke. Blood vessel cells are able to grow and multiply even in the harsh, oxygen-depleted environment of a cancerous tumor. By creating their own pools of ATP, says study collaborator Salvatore V. Pizzo of Duke, the blood vessel cells survive where other cells die.

Angiostatin, by putting the squeeze on the blood vessel cells' source of energy, starves the vessels, whose absence in turn starves the tumor.

Although the drug has raised many hopes, it's difficult to produce. The business end of angiostatin is folded up in pretzel-shaped "kringles," named for their resemblance to Danish sugar cookies, says Pizzo. "The problem is that it's very difficult to produce angiostatin in its native [structure]."

Knowing angiostatin's target enzyme, researchers may be able to create less contorted drugs with the same power. "Anytime you find a binding protein for a therapeutic agent, you immediately think: Could you engineer a smaller molecule that . . . could substitute for or mimic the agent?" says Judah Folkman of Children's Hospital in Boston, who pioneered the study of blood vessel–growth inhibitors to combat cancer.

This class of drugs continues to gain new members. Other Boston researchers report in the same issue of PNAS that they isolated a compound from human cartilage that inhibits blood vessel growth in mice. *—L. Helmuth*