Spice Therapy?

A potential new treatment for cystic fibrosis comes from a surprising source: turmeric, the spice that makes mustard yellow and gives curries their hallmark taste. NIGMS grantee **Michael Caplan** of Yale University in New Haven, Connecticut, found that feeding curcumin (the intense yellow pigment in turmeric) to mice prone to developing cystic fibrosis dramatically cut the experimental animals' death rate. The mouse studies are promising enough that the Cystic Fibrosis Foundation has begun a small clinical trial with curcumin in people with cystic fibrosis.

In cystic fibrosis,thick mucus clogs the lungs and other organs. In most people with the condition, the root cause of the excess mucus is the loss of function of a protein that forms a channel to control the flow of chloride into and out of cells. In diseased cells, policing mechanisms automatically quarantine the channel protein, which hasn't folded properly, to a waste bin where it is later destroyed. With the channel confined, chloride (a component of common table salt) is trapped inside the cells,leading to a thickening of mucus that traps bacteria and causes life-threatening infections.

Based on what Caplan knew about curcumin's chemical properties, he suspected that the spice might be working by interrupting the protein quarantining process. This would let the channel protein—still reasonably effective in ejecting chloride—do its job. Caplan confirmed the hunch with experiments showing that curcumin restored normal chloride flow out of cells. While the findings are encouraging, people should not self-medicate with curcumin, Caplan advises.Scientists do not yet know, for example, if the substance, sold as a dietary supplement, might interact with prescription drugs.—A.D.

Hot Flash News Flash

Tamoxifen (Nolvadex®) is an effective therapy for some types of breast cancer. However, roughly 80 percent of women who take the drug experience hot flashes. While not life-threatening, hot flashes can be so uncomfortable that people stop taking the medicine. To make this cancer-controlling drug tolerable, doctors can treat Nolvadex-triggered hot flashes with antidepressants such as paroxetine (Paxil®).

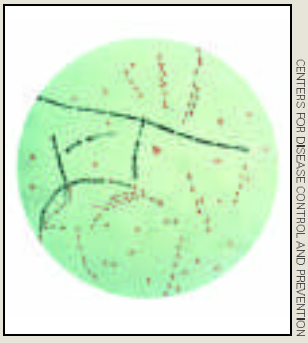
New evidence hints that taking both drugs together may not be such a good idea. NIGMS grantee **David A. Flockhart** of the Indiana University School of Medicine in Indianapolis knew that the body breaks down Nolvadex and Paxil with the same enzyme. He wondered whether taking both drugs together might affect blood levels of either or both of them. To test this, Flockhart and oncologist Vered Stearns of the Johns Hopkins University School of Medicine in Baltimore, Maryland, performed a study with 12 breast cancer survivors who had been taking Nolvadex for at least 1 month and were having severe hot flashes. The researchers gave Paxil to the study volunteers for 4 weeks and then took blood samples.

Women who took both drugs at the same time had substantially lower levels of a key byproduct of Nolvadex, chemical evidence that Paxil does affect how the body processes Nolvadex. But the effects differed among the women depending on their innate capacity to process drugs, which helps explain why Nolvadex's effectiveness can vary among people.Flockhart cautions that until further data become available, the results of his study should not alter treatment recommendations because the health implications are still uncertain at this point.—A.D.

From Hepatitis to Anthrax

The 2001 bioterrorism attacks on the U.S. mail system proved that anthrax can be fatal. Nearly half of those infected in the attacks died, and many survivors continue to face difficulties such as fatigue, shortness of breath, and memory problems. Antibiotics work well if given soon enough after exposure, but once an infection begins, the bacteria that cause anthrax release toxins that can kill a person even after the microbes themselves die. Although new drugs against anthrax toxins are being developed,none are yet ready for use in humans.

NIGMS grantee **Wei-Jen Tang** of the University of Chicago has studied an anthrax toxin called edema factor for several years. He previously determined its atom-by-atom structure and showed how the toxin hijacks normal cell function. In a recent stroke of luck,another researcher who was studying a hepatitis B drug called



CENTERS FOR DISEASE CONTROL AND PREVENTION

Hepsera® read about Tang's work and wondered whether the drug, which mimics a natural biological target of the anthrax toxin, might also work against edema factor. Tang confirmed the hunch,discovering that Hepsera grips tightly to edema toxin and prevents it from damaging lab-grown mouse cells.

If anything, Hepsera appears more potent against the anthrax toxin than in its approved use against a hepatitis B viral protein. Since the medicine is already known to be safe in humans, researchers could potentially test its ability to treat anthrax relatively quickly. Although the drug only blocks the action of one of the three major anthrax toxins, the poisons apparently magnify the effects of each other, so blocking one of them would be of great benefit.—Karin Jegalian

Blocking Bacteria

A well-known complication of surgery is infection, which can be caused by bacteria that are harmless in healthy people but sometimes turn deadly in those whose defenses are down. People hospitalized in an intensive care unit and receiving intravenous fluids are at higher risk of infection because their intestines become leaky and vulnerable to bacterial invasion. Bacteria such as *Pseudomonas aeruginosa* sense this stress and re-program their strategy to attack mode. Instead of growing calmly, they take advantage of the easy entry and make their way into the bloodstream, causing widespread, potentially deadly infections.

NIGMS grantee **John Alverdy** of the University of Chicago wondered if a peace-making approach toward the germs might work. In experiments with mice, he tested whether a waxy material called polyethylene glycol, or PEG,might protect the intestines from bacterial invasion. Alverdy suspected that PEG molecules might serve as a kind of artificial mucous barrier that the bacteria would find appealing, keeping them safely in place. He found that all of the mice that had undergone liver surgery and then received PEG could resist *P. aeruginosa* infection. Alverdy backed up the findings in experiments with isolated human intestinal cells, showing that PEG prevented *P. aeruginosa* from latching onto cells.

If studies in humans have similar results, patients undergoing major surgery may someday be given PEG routinely to coat their intestines and prevent *P. aeruginosa* infection. This approach might also be more ecologically friendly than the prolonged use of multiple antibiotics, which encourages the growth of menacing, drug-resistant bacteria.—K.J.

Reconstructing a Deadly Flu

The "flu," short for influenza virus, strikes millions of people every year. Some years most cases are mild, whereas other years—most notably during the 1918 "Spanish flu" pandemic—the outbreak is deadly. Why the 1918 flu killed more people than died in World War I is still a mystery. To better understand how deadly flu strains arise, scientists examined the molecular details of hemagglutinin (HA), the virus protein responsible for infection.

In a team effort with scientists across the country, NIGMS grantee **Ian Wilson** of the Scripps Research Institute in La Jolla, California, figured out the three-dimensional molecular shape of the HA protein from the now-extinct 1918 flu virus. One of Wilson's collaborators, Jeffery Taubenberger of the Armed Forces Institute of Pathology in Washington, DC, collected genetic material from preserved tissue specimens and from the remains of people who died of the flu in Alaska and were buried in the permafrost. He then pieced together the sequence of the gene for the HA protein and made enough of it in the lab to determine its structure.

Knowing the exact shape of the 1918 HA protein, the researchers were able to compare it to HA proteins from humans, birds, and pigs. They found that the 1918 variety most resembles HA from birds, which suggests that the 1918 flu pandemic possibly arose from a bird virus that was unusually good at infecting people. Viruses passed from birds and other species to humans are rare and potentially very dangerous,since human immune systems are unaccustomed to them and have a tough time fighting them off.—Audrey Huang

These stories describe NIGMS-funded medical research projects. Although only the lead researchers are named, science is a team sport and it is important to realize that many researchers work together to carry out these studies.