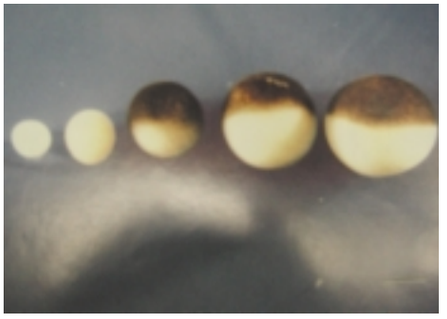
*Explorations and revelations taking place at the medical school*

# WHERE THE LABS ARE KNOTTY PINE

**A WEEK AT MOUNT DESERT | BY SALLY ANN FLECKER**



**LEFT: Around the fire at Mount Desert. RIGHT: Oocytes injected with RNA express normal and mutant ion channels. Students who went on the Mount Desert trip now know why these frog eggs might interest docs.**

If it hadn't been for the mosquitoes, Lestina Clay, MD '04, might have thought she was in heaven. The University of Pittsburgh medical student was one of 24 who capped off their first year of med school by jumping on a plane, the day after finals, to travel to an island off the rugged coast of Maine. They were there for a week to dive into basic science research.

The beauty of the setting dazzled Clay—the laboratory is right on the shore. But what put the whole experience over the top for her was the drama that unfolds bit by bit, every day in the labs of intent researchers: the satisfaction of asking a good question, hanging in there until you have an answer, talking over what the results mean with your colleagues.

The trip itself—to Mount Desert Island Biological Laboratory (MDIBL), a working retreat on Salisbury Cove, near Bar Harbor and Acadia National Park—was an experiment. Ray Frizzell and Mark Zeidel organized and developed the curriculum for the intensive laboratory experience. "This is part of a larger initiative that we're developing to stimulate more students to go into research," says Zeidel, chair of the Department of Medicine.

The decline in the number of physician-scientists—those who will combine clinical practice with research—is cause for concern nationally. "There are often barriers to people becoming involved in research," says Frizzell, chair of cell biology and physiology. Some of it is economic—a med student's debt burden and the uncertainty of research funding play roles. Many times, students just might not have had a chance to catch the bug. "They don't know where to start," says Frizzell.

Clay is a prime example. She majored in social welfare at the University of California at Berkeley, and her exposure to science was limited to the courses she took in order to apply to medical school.

"I had never done research before," she says. "I had no idea what research even meant."

The week on Mount Desert Island would change that.

Study days began early and ended late, often stretching until midnight. Throughout the week, students worked in teams that moved through three lab rotations, each related to the polarized epithelial cell. It's no accident that MDIBL is perched beside the Atlantic. "Fish tissues resemble parts of our organs, such as the kidney," says Zeidel. "But the fish tissues are big. The cells are big. And the effects are huge. So, it allows you to study it easily."

In one project, students worked with frog eggs to study protein expression (specifically epithelial ion channels); this allowed them to consider how protein structure affects function within a specific cellular system. In another, they perfused a shark rectal gland to measure the effect on salt secretion from the gland. After many hours in the lab, the students would present their findings the following day.

There were discoveries—both scientific and personal. Witness the triumph of Hameed Aziz, MD '04. One of the highlights of his week was when his group, after a 13-hour-day in the lab, discovered a protein in a shark. They named it "sunc-18," since it's analogous to a protein called "munc-18" found in mice.

There was also the realization made by Josh Olstein, MD '04. "The week opened my eyes to how much work goes into a discovery," says Olstein. "It's easy to take it for granted when you're just given the results."

And there were intangibles—time spent in beautiful, rustic simplicity (even the lab walls were knotty pine) and the collegiality among faculty and students.

"It's important for students once in a while to be able to have an easygoing conversation over breakfast, lunch, dinner, with a mentor, someone who can provide guidance," says Allyson Pitt, MD '04.

Clay's final impression? She has caught the bug—as long as the mosquitoes stay out of the lab. ■

PHOTOS COURTESY ZEIDEL

# CAN'T MISS A BEAT

## DEFIBRILLATORS GO PUBLIC

BY EDWARD HUMES

John Dellorso, a veteran of the Korean War, marched in a Memorial Day parade this year in Canonsburg, Pennsylvania, proudly carrying the colors of VFW 191. He felt good afterward, maybe a little tired. Then, while riding away from the parade in his car, he collapsed from a sudden cardiac arrest. His heart had stopped beating.

At that moment, a statistical clock began to tick. Four to six minutes following collapse, most people will suffer permanent brain damage; at the ten-minute mark little hope is left for survival. Ninety-five percent of the victims will die. Virtually the only way to save someone in sudden cardiac arrest is by using a defibrillator, which gives an electrical shock to the heart. The sooner the shock is given, the better chance there is of restoring normal rhythmic beating. "Every minute, every second, counts," says Vincent Mosesso, MD '88, assistant professor of emergency medicine at the University of Pittsburgh.

When someone collapses from cardiac arrest, bystanders should call 911 and begin CPR, which plays the crucial role of buying the victim more time, circulating oxygenated blood throughout the body and keeping cells alive, in the hope that medical personnel will soon arrive. But after a call to 911, it typically takes six to eight minutes for an ambulance to arrive on the scene with a defibrillator. For many, help does not arrive soon enough.

Mosesso, medical director of Pitt's new National Center for Early Defibrillation (NCED), believes earlier access to automated external defibrillators, AEDs, would save lives. Police often arrive at the scene of a sudden cardiac arrest before emergency medical services (EMS), so in 1992, Mosesso began a study involving police officers in the South Hills of Pittsburgh. He gave the officers AEDs and trained them in their use. During the three-year study period, police officers were asked to use the AED if they arrived first on the scene. When those police applied the shock, patients survived in 26 percent of cases. They received the shock a mean time of 6.8 minutes after the call to 911. When EMS arrived first, patients survived 10 percent of the time (mean time 9.4 minutes). When the police arrived first, but waited for EMS to use the AED, patients survived in 3 percent of cases (mean time 10.3 minutes).

Mosesso was impressed by his study's results, but far from satisfied. Even if all the police officers in the country had AEDs, that wouldn't be preparation enough for him. It takes time to arrive on the scene. Precious minutes are lost.

What Mosesso wants is for AEDs to be as common as fire extinguishers, to be hanging on the walls of buildings where people live, work, and congregate. He wants the man or woman on the street, who happens to be on the scene of an emergency, to use one, shortening the time from collapse to defibrillation.

Their ease of use helps make his goal feasible. "Not only are AEDs easy to use," says Mosesso, "they are very difficult to misuse."

An AED, which is about the size of a laptop computer, contains retractable pads that adhere to the chest. The pads analyze the heart's electrical activity to determine what action to take. *Do not touch patient. Analyzing rhythm,* the AED may say in an automated voice. In two-thirds of sudden cardiac arrest cases, the electrical patterns are of the kinds that may respond to an electrical shock. If the AED determines a shock is needed, it might say, *Stand clear. Push flashing button to rescue.* When the user pushes the button, an electrical current runs between the electrodes contained in the two pads, attempting to give control back to the heart's natural pacemaker.

Now Mosesso is part of a nationwide trial, supported by a $20 million National Institutes of Health grant, that analyzes the effectiveness of AEDs in the hands of laypersons. There will be 1,000 study sites in the United States and Canada, including office buildings and apartment complexes, golf courses and concert halls. People who live or work at each site, a total of 15,000 volunteers, will participate. Half will be trained in current emergency response techniques, such as contacting 911 and performing CPR. Half will receive AEDs and be trained to use them in conjunction with calling 911, CPR, and other current emergency response methods. Will the people with AEDs save more lives?

Mosesso hopes so. And he's optimistic that, eventually, AEDs will become inexpensive enough (they are currently priced around $3,500) that they will be given as Christmas gifts.

After Dellorso collapsed on Memorial Day, a police officer with an AED arrived on the scene. The first shock had no effect, and the AED recommended another. With the second shock, Dellorso's heart was jolted back into beating. His daughter and son-in-law have since purchased an AED for the Canonsburg police department in his name. ■

FOR MORE INFORMATION: **http://www.early-defib.org**

# THE ENDOCYTOSIS PICTURE SHOW

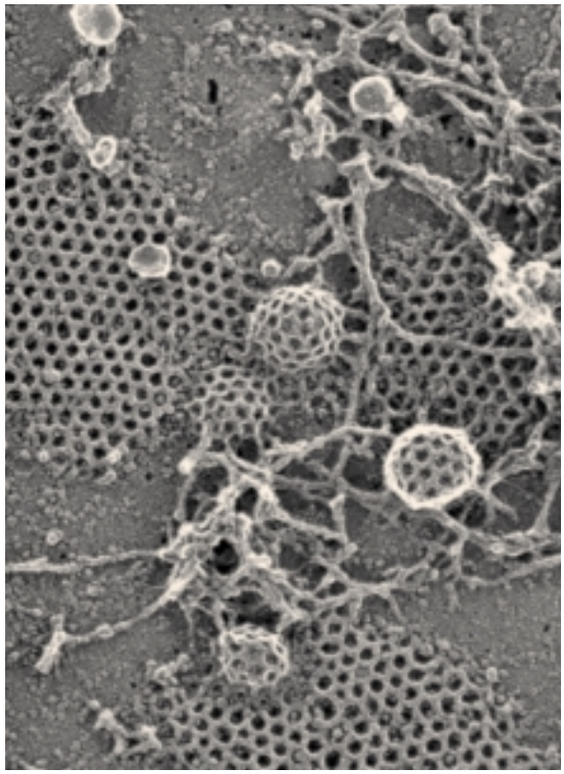
## TRAUB'S DEPTH OF PERCEPTION | BY DOTTIE HORN

Linton Traub keeps a pair of 3-D glasses in his desk. They look like a toy, their shiny lenses, one green and one red, caught in a paper frame. When asked about his work, the assistant professor of cell biology and physiology doesn't take long to bring out the glasses. But first he defines, for the uninitiated, the cellular process that has been the focus of his career for the past decade—endocytosis. It is the most common way cells bring extracellular particles, like nutrients, into the cell. A deepened understanding of such basic cellular biology will leave scientists better poised to tackle a wide spectrum of diseases.

"One of the things I really like about endocytosis is that it's very visually compelling," Traub says.

But the 39-year-old researcher doesn't grab his glasses immediately. First, he paints a picture with words. "If you were suspended, like from a hang glider, over a cell, and you were looking down at the surface of the cell, you'd see these little indentations in the surface," he says. These are the pits involved in endocytosis.

"Then, switch your perspective," he says. "Imagine you plunged into the cell and were inside the cell and were looking up at the membrane, like at the ceiling." Now, he reaches into his drawer. "I'll show you a picture," he says. "See you have to wear these glasses, because it's actually in three dimensions."



**To create this image, researchers broke a cell growing on a piece of glass. They took off the top portion, leaving the bottom—the membrane and its associated proteins—stuck to the glass. Using an electron microscope, researchers could then see what the membrane looks like from inside the cell. Protruding from the membrane are endocytotic pits. By putting a second image of this cell (taken at a slightly different angle) on top of this one, scientists can view the cell in three dimensions.**

From inside the cell, the pit is like a bulbous, intruding growth. The surface of the pit is not smooth or continuous, but like a cage or a honeycomb, a hollow, geometric frame. The 3-D glasses make the geometric bulbs (the endocytotic pits) jump toward the viewer.

Having looked at the pits from inside and out, Traub begins to explain how they work. A protein called clathrin is the fundamental component of the pits. Clathrin is drawn to the site on the cell membrane where a pit will form. First, the clathrin is flat, but then it forms a geometric lattice and starts budding in toward the cell. Caught between the clathrin and the membrane is an AP-2 adaptor. This adaptor is like a mail sorter—it selects from the external environment the particular particles it wants to bring into the cell. Once the AP-2 adaptor has bound to the selected particles, the clathrin surrounds the particles, forming a transport vesicle that breaks off from the membrane. The vesicle, which Traub likens to a mail truck, travels inside the cell, deposits its cargo where it needs to go, then disintegrates.

While these basics are clear, Traub has been working to solve some of the mysteries surrounding endocytosis. One puzzle involves the AP-2 adaptor, which binds to clathrin, but only weakly. Given this weak affinity, how does the AP-2 manage to bring the clathrin to the site on the membrane where a pit needs to form?

Traub helped uncover the answer by looking at the handful of accessory proteins that bind to AP-2. When it's time for a pit to form, these accessory proteins, which also have a strong affinity for clathrin, summon AP-2.

"Accessory proteins together with AP-2 create a much more powerful signal to recruit clathrin onto the membrane than the AP-2 by itself," says Traub. But, once the clathrin has formed the transport vesicle, it must break off. How can it leave when it has such a strong affinity for the accessory proteins?

"Clathrin binds and very quickly forms this lattice," says Traub. "But once it has done that, these accessory proteins depart, because their job was just to bring the clathrin, to make it form the cage."

Each time a mystery is solved, another rises in its place. "These accessory proteins bind to AP-2 and clathrin very well," notes Traub. "So how do they actually disentangle themselves after they've done their job? Actually, we have no clue how they do that."

He believes his microscopic images will help reveal the answer: "You peel away layers at a time." ■

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