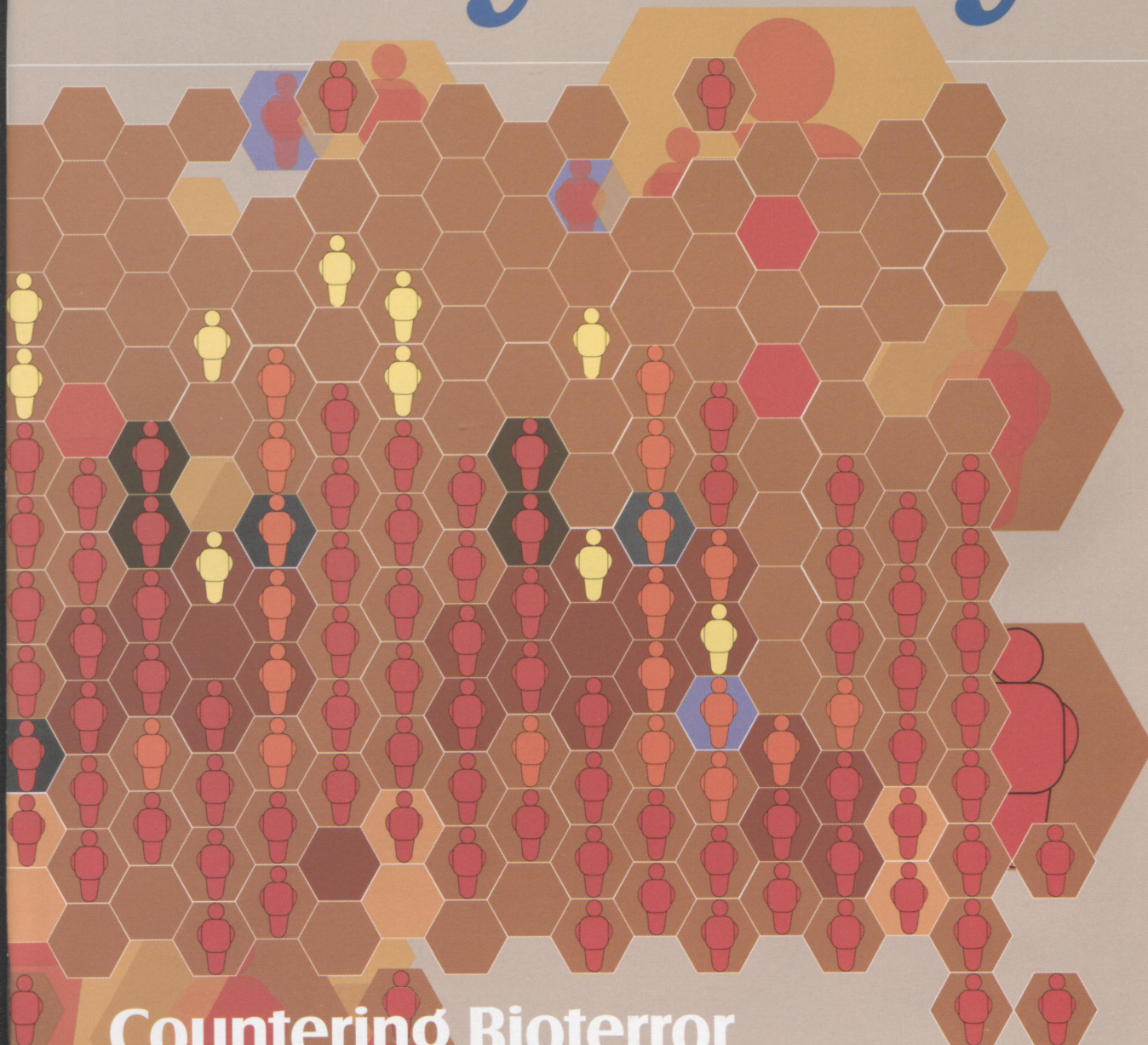


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# Odyssey

University of Kentucky Research

Fall 2002



**Countering Bioterror**  
**UK Scientists Attack**  
**Infectious Diseases**

**UK** UNIVERSITY OF KENTUCKY



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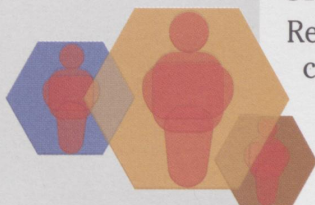
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# University of Kentucky Research Fall 2002 Odyssey



## Cover Story

### Countering Bioterror: UK scientists attack infectious diseases

Researchers at UK are testing a new smallpox vaccine for the military, making fundamental discoveries about the bacteria that cause plague, and finding better ways to protect animals, fruits and vegetables from microbes.

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### Regenerating Hope: Spinal Cord Research at UK

A team of researchers and clinicians in a wide range of disciplines is studying every aspect of spinal cord injury, work that one day may revolutionize the way physicians treat these injuries.

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### John Jacob Niles Has a New Kentucky Home

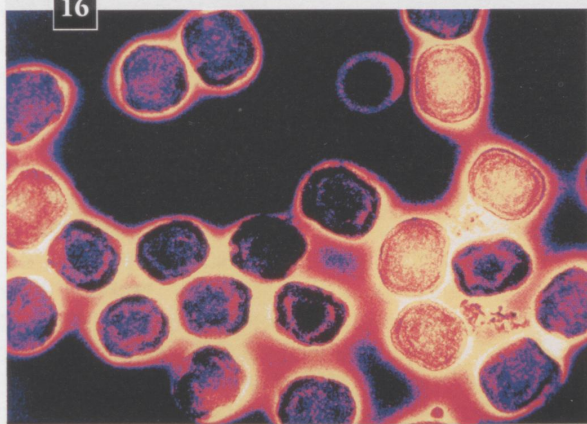
An extensive collection of this Kentuckian's songs, writings, and instruments has a permanent home in the new UK center.

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## Research Outreach

Using Literature to Teach Math and Science

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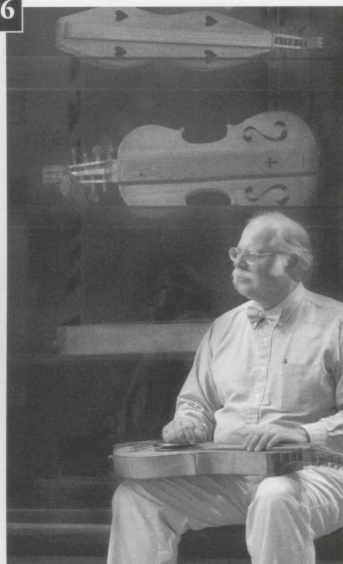
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It's Good to Be King

He didn't set out to link the behavior of male primates with the behavior of world leaders, but years of research led this emeritus psychiatry professor to that unmistakable conclusion.

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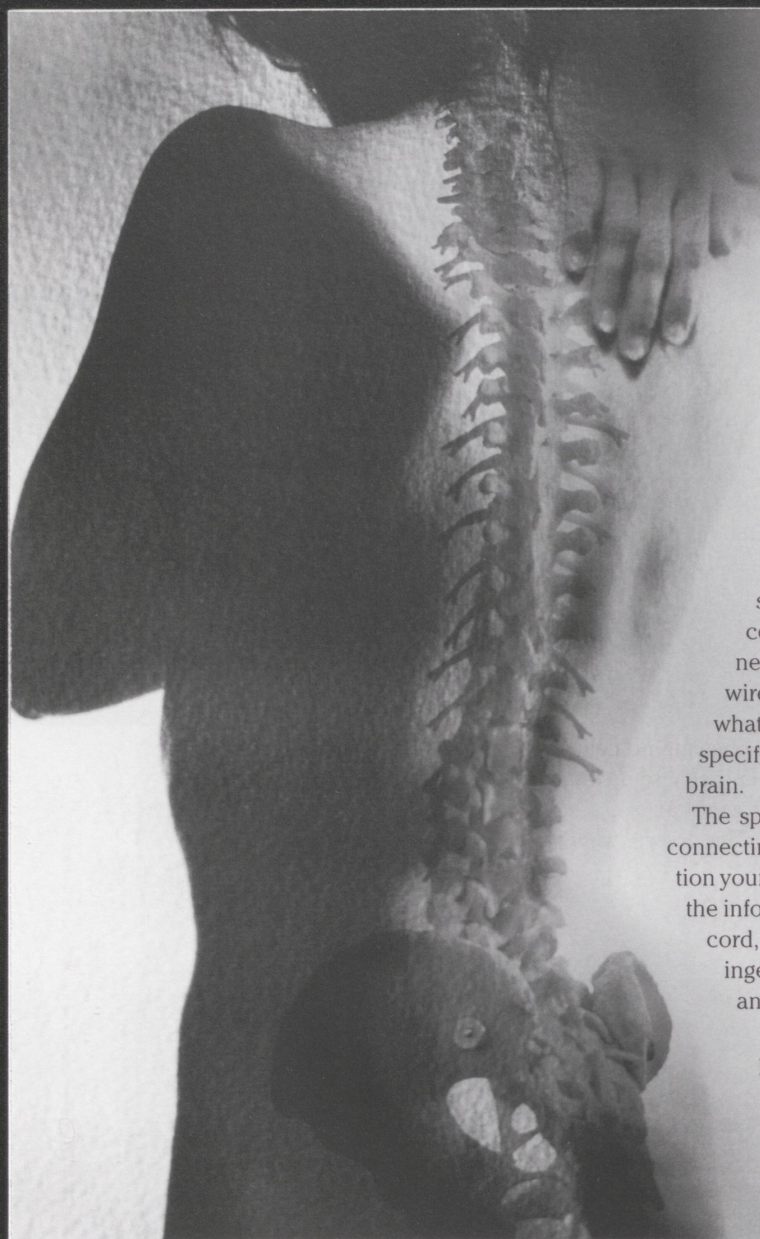


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Imagine scattering a bunch of computer parts on a table, leaving the room for a while, and the parts magically assembling themselves into a functional computer. On the much more sophisticated level of neuron growth in a fetus, this is roughly how the nervous system develops.

During fetal development, the nervous system generates several billion neurons, and these neurons make trillions of connections. Within the spinal cord—the largest nerve in the nervous system—millions and millions of individual cellular wires form little bundles. Operating independently and following what neurologists call guidance proteins, each bundle makes specific connections to different regions and cell populations in the brain.

The spinal cord is the physiological equivalent of a smart cable connecting the body to the brain—your CPU. All the sensory information your body gathers travels to your brain through this cable, and all the information your brain translates travels back through the spinal cord, which assigns this information to specific muscles. It's an ingeniously complex system that allows us to stand, move, turn, and bend.

Most of us take these actions for granted—but not the approximately 11,000 people in the United States who suffer from spinal cord damage each year as a result of accident or disease. If the neurons in the spinal cord don't fire properly, the brain gets less information to translate, and in the case of severe injury, no information at all; so it can't relay instructions to the muscles. The location of the injury is important,

WRITTEN BY  
Debra J. Gibson

# Regenerating Hope: Spinal Cord Research at UK



too: the higher it is on the vertebral column—the closer it is to the brain—the more it limits what a person can do and feel.

Just a decade ago scientists believed that little could be done to help a person with a spinal cord injury. They thought that once damaged, neurons could not be repaired. This view changed in 1990 when a high dose of intravenous methylprednisolone, administered within eight hours after injury, was shown to improve motor function. Methylprednisolone, a synthetic steroid which has been used for the last half-century primarily as an anti-inflammatory agent, is the only drug currently approved to treat spinal cord injury.

Today, the University of Kentucky is well on its way to becoming a leader in spinal cord research. The Spinal Cord and Brain Injury Research Center (SCoBIRC) was established here in 1999 to encourage multidisciplinary research, and last July nationally known researcher Ed Hall, who is credited with developing high-dose methylprednisolone therapy, was named to head the center. He joins 20 faculty members and a team of research assistants and clinicians from a variety of disciplines who are studying every aspect of spinal cord injury, work that one day may revolutionize the way physicians treat these injuries.

### Limiting the Damage

James Geddes, an associate professor in the Department of Anatomy and Neurobiology at UK, focuses his research on the crucial hours following a spinal cord injury. "We can't prevent

the initial damage which occurs milliseconds to seconds after the incident, long before emergency personnel arrive, but we can try to limit the damage in the hours that follow," Geddes says.

Secondary events to the injury are responsible for much of the damage to neurons, he says. One such event is calcium overload, which results in the activation of calpain, an enzyme that is triggered by elevated levels of calcium and then begins chewing up cellular proteins. However, because a certain level of calpain is important to normal cell function, Geddes doesn't want to block it completely.

"Currently, we don't have good calpain inhibitors that can walk this fine line," he says. "And the ones we have must be injected directly into the tissue and are only active for about two hours, so you have to keep re-injecting them."

Geddes is in the early stages of developing an improved inhibitor that will be 10 times more potent than current inhibitors and possibly be given in pill form, making it easier for emergency personnel to administer. He is using synthetic calpain inhibitors as well as gene therapy to control the level of calpain in the spinal cord. A combination of calpain inhibitors with other therapeutic approaches, including antioxidant treatments and anti-inflammatory interventions, could effectively limit the secondary damage following injury.

Geddes predicts that combined therapies targeting specific mechanisms will offer greater neuroprotection and functional improvement than the currently approved treatment, the use



Edward D. Hall, UK's new director of the Spinal Cord and Brain Injury Research Center (SCoBIRC), discovered that high-dose methylprednisolone was effective in the treatment of acute spinal cord injury, and today it is the only drug approved for the treatment of this injury. UK established SCoBIRC in 1999 to promote studies that might ultimately lead to a functional repair of the injured spinal cord and brain. The center is funded in part by the Kentucky Spinal Cord and Head Injury Research Trust (KSCHIRT), which receives \$12.50 from each speeding ticket fine to help pay for spinal cord and head injury research. "Kentucky has made a real commitment in this area through KSCHIRT," Hall says. "Because of the excellent faculty already in place and the commitment of the university and the state of Kentucky, UK is the best place imaginable to pursue research aimed at spinal cord and brain injury."



**Some 10,000  
Americans  
sustain spinal-  
cord injuries  
every year  
from car  
accidents  
(44%),  
gunshot  
wounds or  
other violence  
(24%),  
falls (22%),  
or sports  
(7%), largely  
diving.**

"We can't prevent the initial damage which occurs milliseconds to seconds after the incident, but we can try to limit the damage in the hours that follow."

—James Geddes



of the synthetic steroid methylprednisolone. "But this drug," he says, "doesn't target calpain. There are drugs available that do inhibit calpain, but they aren't specific for it. And unfortunately, high concentrations of these drugs are required for them to work."

### **Reestablishing Lost Function**

George Smith, an associate professor in the UK Department of Physiology, is interested in the chronic phase of a spinal cord injury—a few weeks later when the person's condition has somewhat stabilized. He hopes that his research will lead to ways to help people reestablish lost function.

"During the acute phase of the injury—a few hours to weeks—the neurons die a slow, progressive death," Smith says. "My lab studies the later stage of injury, after all the cells have died and the injury has reached a steady state. We want

to go in and try to induce the axons to re-grow and reconnect, to try to get the wound to heal appropriately." Axons are nerve fibers that, like wires, extend long distances to connect one nerve cell to another.

Smith says there are several potential reasons why axons fail to regenerate. One mechanism is as old as the body itself—the overproduction of inhibitory molecules that are important to the healthy segregation of axons during fetal development and that stop axons from growing in the adult.

He explains that some of these molecules that are produced during development may be reactivated after a traumatic injury. "For instance, scientists know that meningeal cells, non-neuronal cells that cover the brain and spinal cord, actually migrate and infiltrate the wound after an injury to form scar tissue. But these and other non-neuronal cells also express some of the inhibitory molecules that may restrict axon growth."



Smith's research is focused on reducing this inhibition. "We're trying to neutralize the inhibitory molecules produced by these cells or prevent their migration into the wound cavity. We're also trying to find molecules that bind to the inhibitory molecules and inactivate them or make them switch sides, from an inhibitory molecule to a growth-supportive molecule," he says.

Smith is also involved in transplant targeting. His goal is to understand the mechanisms that lead to axon guidance and develop a therapeutic intervention to entice severed axons to re-grow to precise locations. To do this, he uses recombinant adenoviruses, replication-defective viruses used as a vehicle to transfer genetic material into nerve and glial cells (non-neuronal cells in the brain). Using this method, he can create a pathway to direct the growth of axons, and he has already had some noted success in this aspect of his work.

"We establish pathways," he says. "If the axons follow the pathway, they

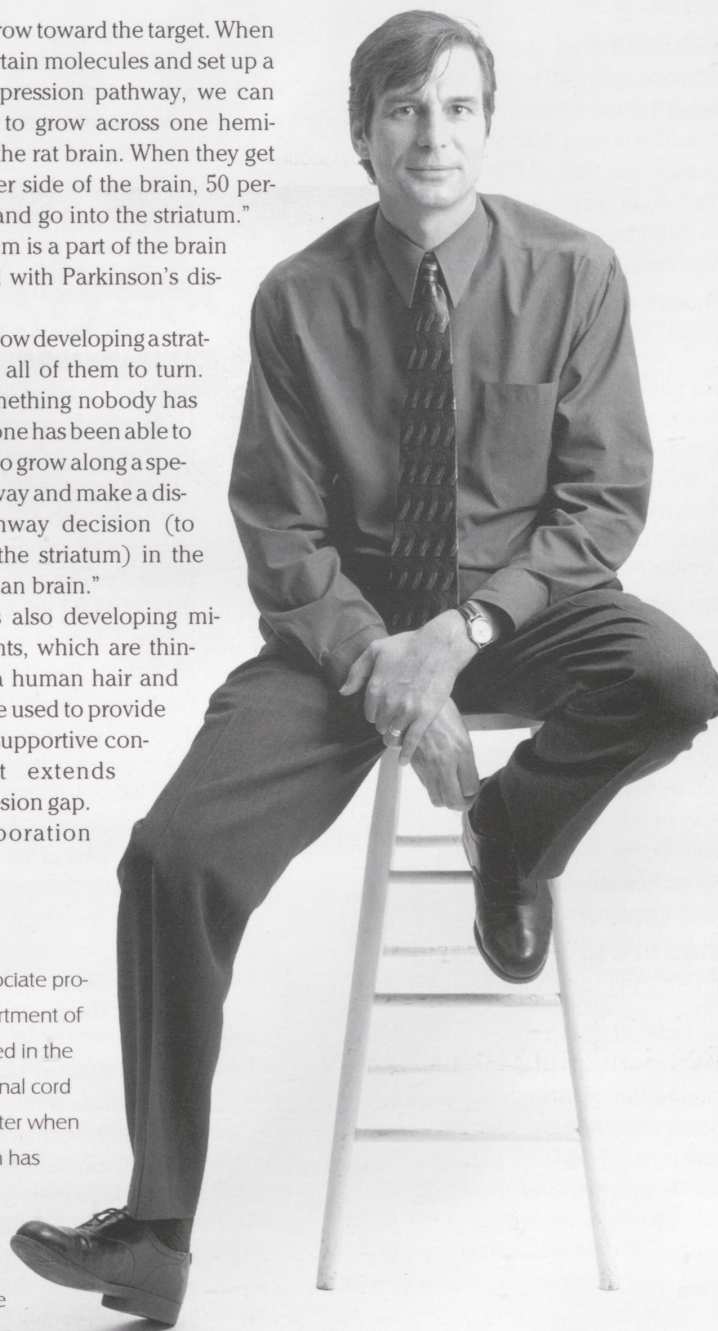
turn and grow toward the target. When we use certain molecules and set up a certain expression pathway, we can get axons to grow across one hemisphere of the rat brain. When they get to the other side of the brain, 50 percent turn and go into the striatum."

The striatum is a part of the brain associated with Parkinson's disease.

"We're now developing a strategy to get all of them to turn. This is something nobody has done. No one has been able to get axons to grow along a specific pathway and make a discrete pathway decision (to turn into the striatum) in the adult human brain."

Smith is also developing microfilaments, which are thinner than a human hair and that can be used to provide a growth-supportive conduit that extends across a lesion gap. In collaboration

George Smith, an associate professor in the UK Department of Physiology, is interested in the chronic phase of a spinal cord injury—a few weeks later when the person's condition has somewhat stabilized. He hopes that his research will lead to ways to help people reestablish lost function.





#### Cervical Nerves

Head, Neck  
Diaphragm  
Deltoids, Biceps  
Wrist Extenders  
Triceps  
Hand

#### Thoracic Nerves

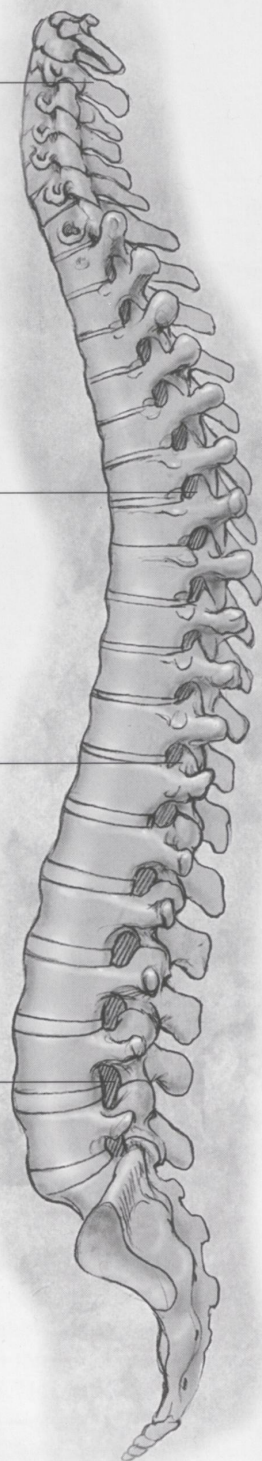
Chest Muscles  
Abdominal Muscles

#### Lumbar Nerves

Leg Muscles

#### Sacral Nerves

Bowel, Bladder  
Sexual Function



with colleagues at U.T. Southwestern Medical Center in Dallas, he has developed a technology for fabricating FDA-approved polymers that dissolve over time and, as they dissolve, slowly release drugs. This tissue-engineering technology has broad applications, including wound healing within the spinal cord, as well as in other tissues.

"Here you have a very complicated system that is broken," Smith says. "Well, I've always liked the challenge of fixing broken things, and regeneration is a very intriguing challenge."

### Improving the Quality of Life

While Smith is focused on long-term strategies to rebuild function, James Abbas, formerly in UK's Center for Biomedical Engineering and the Department of Physical Medicine and Rehabilitation and now at Arizona State University, is using current technology to help improve the quality of life for those with a spinal cord injury.

With his research team at UK, he was involved in a pre-clinical trial using a neuromuscular stimulation device about the size of a pager that can help people with spinal cord injuries stand. Nationwide, 12 people have the implanted device, which was developed at Case Western Reserve University and the Cleveland Veterans Affairs Medical Center.

Here's how this device works: It is surgically implanted in the person's abdomen, and eight electrodes from the device are attached to muscles in the upper legs and lower back. When the person wants to stand, he or she activates the device with an external trigger. It sends an electrical signal via radio frequencies to the stimulator, which causes the muscles to contract and allows the person to stand.

Abbas is quick to point out how important this seemingly simple movement is. "One of the biggest potential complications for people with a spinal cord injury is pressure sores," he says. "Some people don't have a lot of padding between the bone and the skin. When someone is sitting, pressure between the bone and the seat can cause a sore to develop under the skin. This can happen very quickly, in a matter of minutes. If these sores get bad enough, the person can end up in a hospital for months while the sore heals."

Being able to stand could greatly reduce this problem. It could also enable those with a spinal cord injury to transfer from a wheelchair without help, improve their muscle tone, and give them the ability to reach for items. In short, it increases their independence, often boosting self-esteem as well.

And this is merely a starting point as far as the potential capabilities of this system. "For the past several years, we've been focusing on how we can make the system more functional, trying to come up with ways that will allow people to use their hands more and stand longer," Abbas says.

But even such a basic system is an exciting advance for many, including



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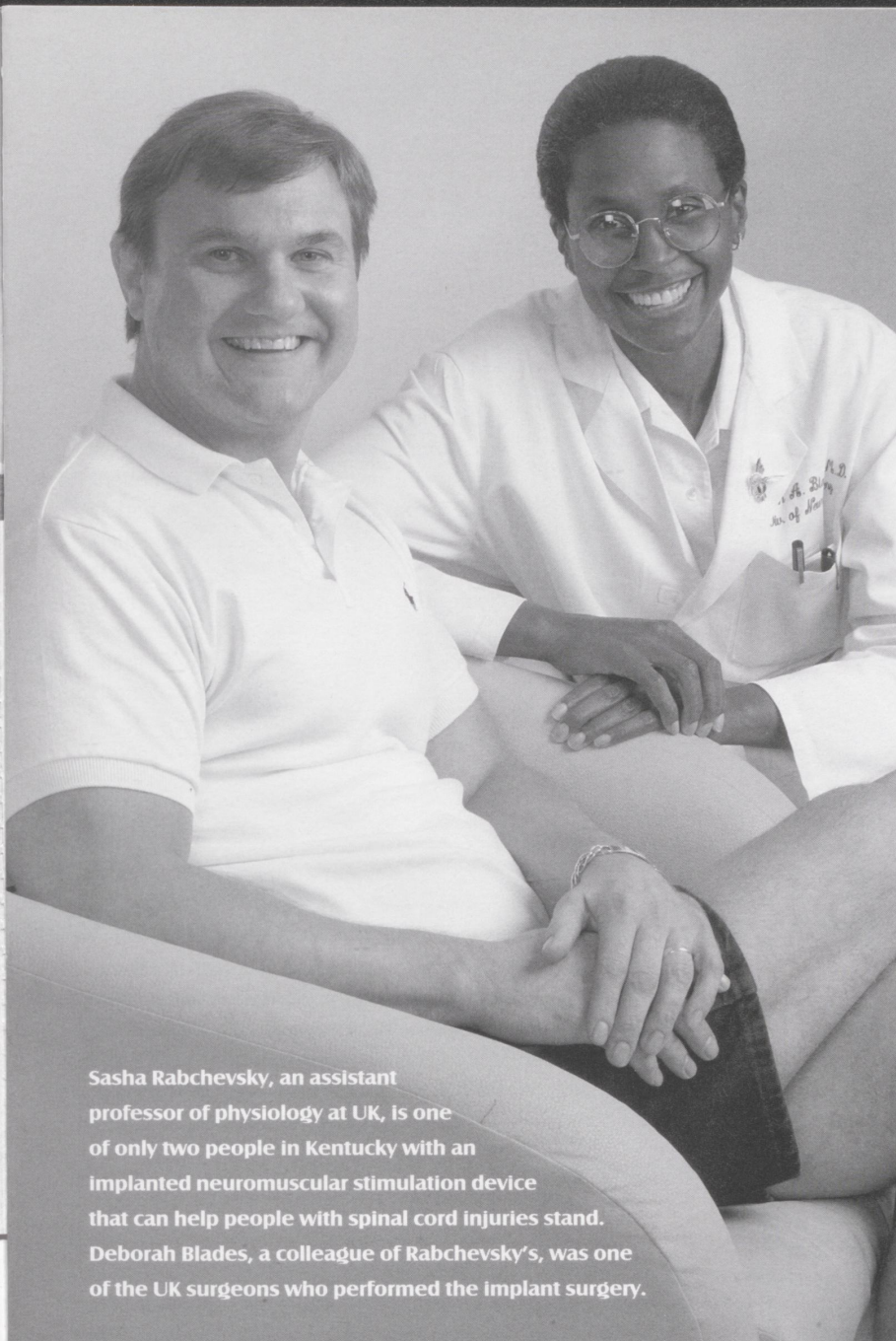
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**Sasha Rabchevsky, an assistant professor of physiology at UK, is one of only two people in Kentucky with an implanted neuromuscular stimulation device that can help people with spinal cord injuries stand. Deborah Blades, a colleague of Rabchevsky's, was one of the UK surgeons who performed the implant surgery.**

Alexander "Sasha" Rabchevsky, an assistant professor in the Department of Physiology at UK and one of only two people in Kentucky with the implanted device.

"I had a motorcycle accident in the summer of 1985 when I was 19," Rabchevsky says. "Ironically, it was just a week before my football camp started. [He was a stand-out high school football player.] There's no doubt that my

spinal cord injury from that wreck drove me into the field of neuroscience. Before the accident, I was a pre-med student in college, but with a 2.2 GPA," he laughs. "After the accident, armed with a sharpened interest, I brought this up in one semester to a 3.0—even after missing an entire academic year for rehabilitation."

Rabchevsky had the operation last January, and he says that an important

factor in deciding to have the surgery was because one of the surgeons who would operate on him, Deborah Blades, was a colleague and personal friend. After coming to UK in 1993, she worked with Rabchevsky (and Stephen Scheff, a professor in the Department of Anatomy and Neurobiology) on several research projects.

"I really enjoyed collaborating with Sasha and Stephen," Blades says, "but my interest was always in making the leap from the laboratory to clinical applications. I had worked extensively on functional-electrical stimulation during my residency at my alma mater, Case Western, so that's how it all came together with Sasha."

Blades says that Rabchevsky's operation, which was done at Case Western, took a lot less time—12 hours—than she and the medical staff in attendance had thought it would. The procedure involved making 13 incisions at eight different points in the body and attaching electrodes to various muscle groups from the device itself, which was implanted in the abdomen. "Things just moved so smoothly that day," she says, "it was great. And all the way through, Sasha's been an outstanding patient—the best!"

Since his operation, Rabchevsky has not only been able to stand for longer and longer periods of time, but has also been able to take his first steps since the accident 17 years ago. He says that the greatest motivating factor in deciding to have the implant was so that he could stand up and kiss his wife, which he says was a "fine moment."



## Combining Therapies

Rabchevsky undergoes therapy each day and works out to maintain his athletic physique, but he spends most of his time in the lab, attacking the problems of spinal cord injury under a microscope. Most of Rabchevsky's research involves combinatorial therapies, meaning that he is looking for ways to use the innate mechanisms of the body along with various drugs to enhance healing processes in the spinal cord. The ultimate goal is functional recovery after injury.

Recently, the compound he has been working with is basic fibroblast growth factor, or bFGF. He is attempting to use this drug in combination with standard methylprednisolone treatment in order to prevent the spread of the initial damage throughout the spinal cord. "What we're trying to do, using rats as a model, is use a drug that has been shown to be beneficial for cell survival and growth—bFGF—and combine it with what is now being used clinically, methylprednisolone. Our hope is that the two will work synergistically to further improve recovery," Rabchevsky says.

"Interestingly, rats with a spinal cord injury can gradually walk over time—not completely normally, but they can walk—whereas a human with a similar type of injury can't," he says. "We are trying to tap into whatever mechanisms

Rabchevsky cites the example of a professional football player named Derrick Thomas, who was paralyzed from a car accident. Two weeks after the accident, during his recovery, he was being transferred from his bed to a chair. He had an autonomic dysreflexia episode, had a heart attack, and died.

"This was a healthy 33-year-old, six-time Pro Bowl athlete in the NFL," he says. "Nobody really knows why this occurs, or why it occurs only in people with high thoracic spinal cord levels of injury but not lower levels. So I am studying the possible mechanisms and nerve pathways that may contribute to this life-threatening condition."

Rabchevsky's research on dysreflexia involves injecting adenoviruses, replication-defective viruses, into injured spinal cords of rats. These viruses can be designed to encode special growth factors as well as growth inhibitors that may alleviate autonomic dysreflexia after a spinal cord injury.

He is also very interested in a cell called microglia.

"It's a unique cell in the central nervous system," Rabchevsky says. "It's very enigmatic because people don't know exactly what its normal function is. When the central nervous system is disturbed—from disease or trauma—microglia are immediately activated and they mobilize to the site of injury. For many years, people associated them with the bad guys: 'Look, there's death and destruction, and there's microglia.' But it

**The great majority of people with spinal cord injury are men—more than 80%, and 44% of them age 16-30.**

rats have that allow them to do that. If we can figure out what the mechanisms are, perhaps we can apply it to human beings."

Autonomic dysreflexia (abnormal autonomic reflexes) after a spine injury is also a major focus for Rabchevsky. With this condition, there is no descending influence from the brain, and the autonomic nervous system goes haywire: the system below the injury is ready to go, but there's no command.

"When normal bodily reflexes go unchecked, any painful sensation to the body below the level of injury—even something as minor as an ingrown toenail—can lead to elevated blood pressure, a lowered heart rate and a serious state of anxiety. The brain can't send any messages down the spinal cord to settle the unconscious nervous system," he explains.

turns out that microglia might be the good guys, trying to augment self-repair processes. My work, along with the work of others, has shown that microglia in the injured rat spinal cord are actually pro-regenerative. They potentially secrete molecules that can actually help guide regenerating axons.

"Again, this is a combinatorial approach," he says. "I want to extend my initial studies and fully characterize how microglia help to promote regeneration in the injured spinal cord."

"There's not going to be a magic bullet," he says of treatments and methods used to study spinal cord injuries. "It's not going to be one answer or one intervention. We have to attack this problem through multidisciplinary approaches, incorporating basic investigations into the cellular and molecular mechanisms that translate into improving the quality of life for those who are paralyzed." ■



Sara Moore and Bill Bintz have an extensive collection of award-winning children's books for use in their current project, but both agree on what they call their "mantra": "We're not about collecting books. We're about connecting books to meaningful curriculum."



WRITTEN BY  
Jeff Worley

**T**he kids in the children's section at Joseph-Beth Booksellers in Lexington must wonder about Bill Bintz and Sara Moore. The two UK College of Education professors can be found there often, excitedly passing new books back and forth and piling up the "gotta haves."

"Sara, have a look at *One Woolly Wombat!* This might go along nicely with *Bat Jamboree*—see what you think."

"Great! And take a look at this one, Bill—*Counting Crocodiles*. Maybe a companion to *One Cow Laughing?*"

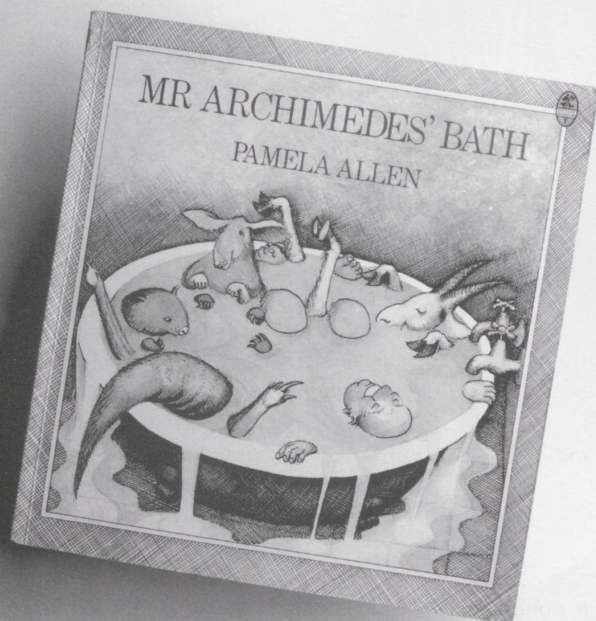
But for the "biggest kids in children's books," as Bintz refers to the two of them, it's all in a day's work.

"When Bill and I go to a conference, we're all over any used bookstores we can find," says Moore, who holds a Ph.D. in gifted education from the University of Virginia. "He's looking for engaging narratives, and I'm focusing on how accurate the math and science are."

Such fieldwork is the basis for a collaborative project designed to support teachers in learning to use high-quality and award-winning children's mathematical and scientific principles. The project, which is being funded by an Eisenhower Grant, is a collaboration between UK and the Appalachian

# Using Literature to Teach Math and Science





Rural Systemic Initiative. During the grant period, from January 2002 to June 2003, Moore and Bintz will work with approximately 75 teachers in grades four through eight from 35 counties in Eastern Kentucky.

"Many children don't have a context for understanding science and math," says Bintz, who came to UK from James Madison University in 1997 and who specializes in inquiry-based learning and teaching, reading across the curriculum, and curriculum development. "Good literature gives them that context and 'eases' them into the math and science. Children think in narrative terms, so we're simply building on that strength."

He reaches up to one of several long shelves of children's books in his Dickey Hall office and pulls down *Sir Cumference & the First Round Table* by Cindy Neuschwander. Bintz explains that in this book Sir Cumference's land is surrounded by a tribe called the Circumscribers. Sir Cumference is married to Lady Di of Ameter and they have a son named Radius. "This is clearly an engaging narrative that young children can tap into. They're drawn into the story and along the way learn some basic mathematical principles," Bintz says.

He recalls a very satisfying incident that followed from a classroom reading of this book when he was visiting an elementary school. "One boy came in the next morning and said, 'Hey, Bill, guess what? I'm not a Radius!' He explained that he had gone home and stood next to his mother. He wasn't half her height yet, so he knew he wasn't a radius. This was an immediate real-world application to what the boy had just learned."

Another very useful book, Moore says, is *The Warlord's Beads* by Virginia Walton Pilegard, which illustrates for young children a method of counting that's ancient and time-tested: the use of an abacus.

"The main character is a boy whose father is the chief counter for the warlord. But people keep interrupting the father, which causes him to lose count," Moore explains. "So the warlord starts thinking his bead-counter is shorting him, that's he's being cheated, and this clearly worries the boy." But the father decides to put the beads on a stick, and this solution saves the day. The counting can now be referenced. "A child reading this will naturally identify with the boy in the story, so there's a clear context for the importance of counting and a methodology."

This book and previous work Moore has done in trying to help elementary-level teachers teach math led Moore and Bintz to develop a "hands-on" session for teachers in first and second grades. In explaining what this session involves, Bintz recounts a conversation he had with his daughter as they waited to board a plane.

"I was taking my daughter Madrean, age 14, with me to a professional conference, but she didn't know what it was about. She asked, 'Dad, what are you and Sara going to do there?' 'Well,' I said, 'we're going to go to a conference for math teachers, and first we're going to read this children's book called *The Warlord's Beads*. Then Sara and I are going to pass around a big box of Fruit Loops—all different colors—and different-colored pipe cleaners, and then we have this square card stock where we've taken out the center except for about a two-inch perimeter.' 'What are you doing all that for?' she asked. 'They're going to make abacuses in this session, and then the teachers will go back home and help children learn mathematics.'"

"My daughter pan-faced me, looked me right in the eye, and, in a voice much louder than it needed to be, said, 'And how old are you?'"

Moore admits that this conference session was good fun, which she says is exactly the point. "We're using the baseline of play as a teaching tool, but for us this is serious play," she says. By using a self-made abacus in the classroom, teachers can help kids learn about number sense and systems, place value, and re-grouping. "This is especially valuable for kids who are more visually oriented," Moore adds.

And though play is an important ingredient in the mix of early childhood learning, Bintz and Moore are very serious about their methodology. What they would like to see, in fact, is nothing less than an entirely different approach to the teaching of math and science in the elementary-school classroom, one in which children's literature would take precedence over traditional textbooks.



## Research Outreach

"If I were teaching math and science, I would still have a textbook in the class, but I'd use it merely as a reference tool—to look up facts or a summary of key words," Moore says. "Ideally, the shelves of my classroom would look like this," she says, gesturing to the hundreds of children's books that line Bintz's shelves in his UK office. "Here is a collection of wonderful, award-winning literature, many of these books fabulously illustrated as well. Why in the world *wouldn't* I use them?"

Bintz admits that several teachers he's spoken with have had misgivings about this approach. Some are worried that despite the interest that would be generated by using children's literature, mandated standards might suffer. And some teachers are frankly uneasy about relegating the textbooks they've been using for so long to merely a supporting role.

"In thinking about our approach," Moore explains, "we looked at national standards and Kentucky core content to make sure these goals would be met. We're acknowledging these standards but saying, 'Look how rich books like these can support the attainment of these standards.' And ordered in a sequential way, these books can allow teachers to make some sophisticated decisions about when individual students are ready for different principles of math and science."

Organizing dozens of books into such a sequence was a time-consuming but essential part of this project. Out of these efforts, several color-coded "text clusters" evolved, linking the stories to various scientific and mathematical concepts. One figure, for example, shows books that illustrate counting up,

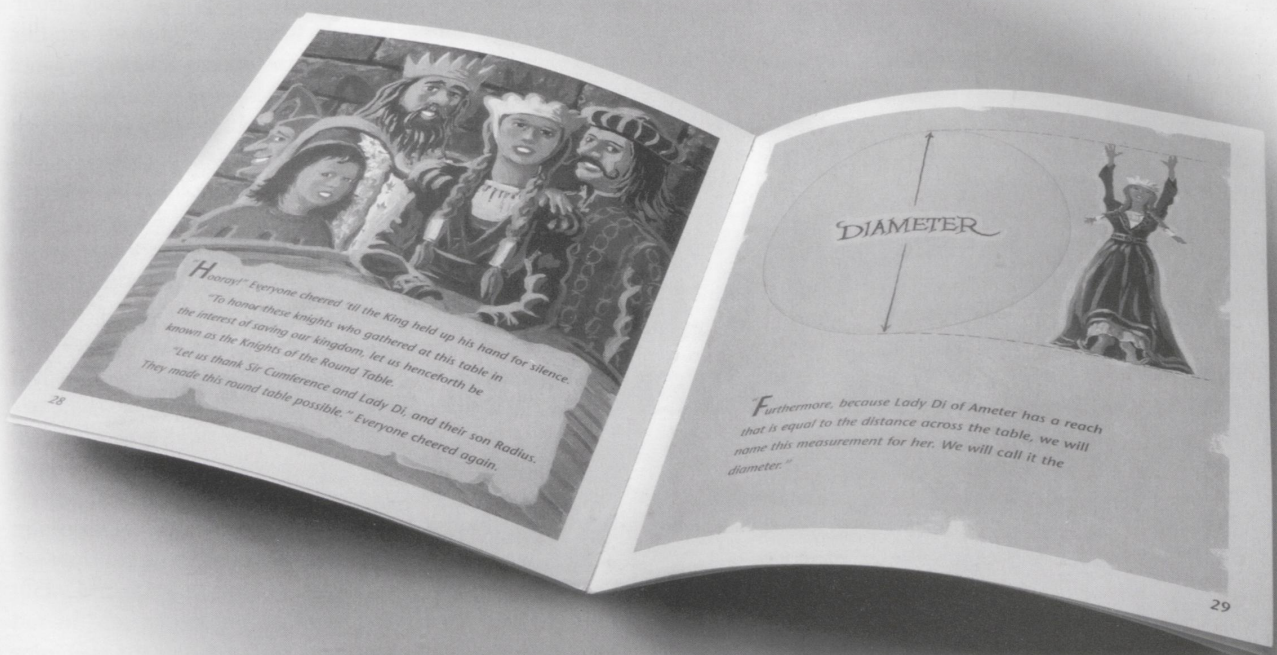
counting down, the sum of a series of numbers, grouping, and skip-counting. Another figure lists literature related to shapes and measurement; and a third lists books that can lead students to an understanding of reasoning, topology, and dimensionality.

This approach may sound tantalizing for many elementary school teachers in Kentucky, but how many schools would be willing and able to buy—and continue to buy—these books?

"Schools can build libraries of these books; they just have to do it over time," Bintz says. "The textbook allocation that comes from the state can be used for trade books like this. The stipulation is that the money has to be spent on instructional material, so buying these books would certainly be legitimate."

"If I were a sixth-grade science teacher teaching 100 kids," Moore says, "I could buy one set of 25 textbooks and instead of buying the other 75, I could spend that money on a collection of literature. The textbooks would still be there in the classroom, but I'd also have a collection of literature that I could continue to build. For instance, I would use *Mr. Archimedes Bath* by Pamela Allen to teach displacement, experimental design, and some history of science."

In trying to garner support for this approach, Moore and Bintz initially modeled this method last January with a group of "teacher-partners," classroom teachers in the 35-county area who have been temporarily released from their classroom duties. And this fall, Bintz and Moore plan to invite every school principal in the designated area to a meeting to discuss and model their approach. ■





**T**here is no flash of light, no mushroom cloud, no smoke, no smell, no taste. No warning.

It will take days, weeks, or even months before we discover a microscopic bomb has been detonated and its contagions are spreading undetected. Bioterrorism is insidious, and that fact gives it the power to hold us hostage.

Our innate fear of disabling and deadly infections is driving us to defend ourselves, through reorganizing government surveillance, rebuilding public health infrastructure, increasing public awareness, and developing better vaccines. And the U.S. Centers for Disease Control and Prevention, in an effort to focus on the most likely and deadly threats, compiled a list of "Category A" biological agents: anthrax, botulism toxin, plague, smallpox, tularemia, and viral hemorrhagic fevers.

As the anthrax outbreak of last October illustrated, public education is one of the key steps to reduce the panic associ-

ated with infectious diseases. And one important part of that education is gaining basic biological knowledge about these bugs.

The CDC's hit list includes two main types of microbes: bacteria and viruses. Anthrax, plague, and tularemia (as well as other threats like pneumonia and tuberculosis) are caused by bacteria. Bacteria differ from viruses in four important ways: they are far larger, more complex, they reproduce by splitting in two, and only about one percent of all bacteria are harmful. Antibiotics can destroy bacteria; however, misuse and overuse in humans and

# COUNTERING UK SCIENTISTS ATTACK BIOTERROR: INFECTIOUS DISEASES



W R I T T E N   B Y  
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animals have lead to mutated bugs that resist multiple antibiotics that were effective weapons against them just a few years ago.

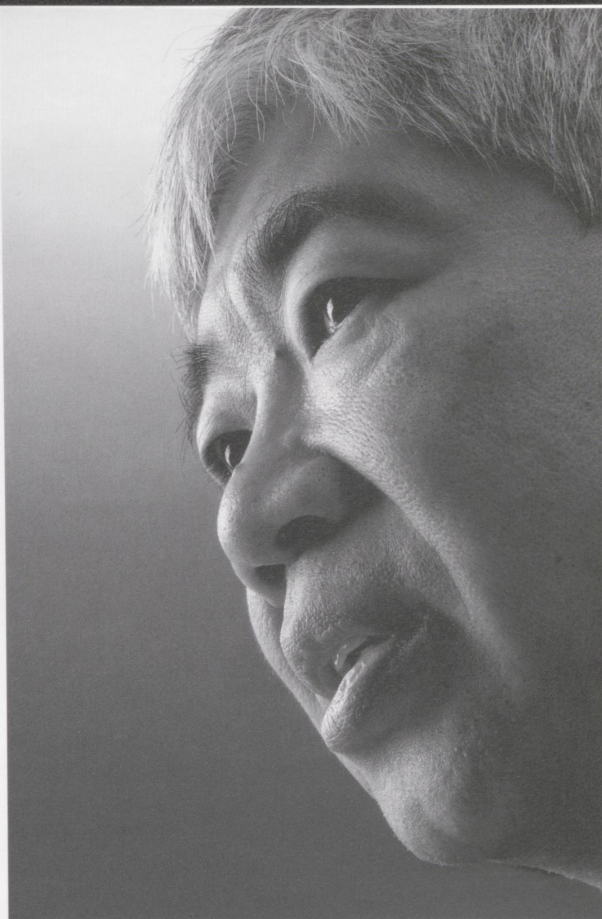
Smallpox and viral hemorrhagic fevers like Ebola (as well as the common cold, influenza, and HIV) are caused by viruses. Viruses are parasites; they can't reproduce without commandeering the genetic machinery of a host cell. Viruses mutate when they multiply, and antibiotics can't kill them. Vaccines and a limited number of antiviral drugs are our weapons against viruses.

Research to fight these infectious microbes is under way in labs all over the world, and the University of Kentucky is making its mark with a number of bioterror-related studies. UK scientists are testing a new smallpox

vaccine for the military (see p. 16), making fundamental discoveries about the bacteria that cause plague (p. 20), and finding better ways to protect animals, fruits and vegetables from microbes (p. 23).

### **Bioterror in the Bluegrass**

Lexington, Kentucky, is not likely a high-priority target for bioterrorists, says Cliff Tsuboi. "It would be more likely that we get caught in the crossfire—catch the secondary effects of an attack on a large city," says Tsuboi, a retired lieutenant colonel in the U.S. Army Reserve who has a doctorate in biopharmaceutics from UK and who is a specialist on biowarfare and bioterrorism.



"If you look at the history of biological warfare, you see it's not very efficient, at least in terms of causing the instantaneous death of thousands of people," says Cliff Tsuboi of UK's Patterson School of Diplomacy and International Commerce. "It's designed mainly to breed panic and terror."

But Kentuckians traveling home by plane could bring infectious agents with them. "If bioterrorists wanted to infect large numbers of people, they'd pick an agent that's transmissible, like smallpox, and put it on an airplane," he says. Smallpox can be spread from person to person by something as simple as a cough. On a plane the deadliness of such a virus is multiplied by the re-circulated air.

"They'd target major hubs like Chicago, Denver, Atlanta, New York, L.A.—where people go off in all directions. There'd be rapid dissemination, probably within 48 to 72 hours," Tsuboi says.

John Stempel and Robert Pringle, Tsuboi's colleagues in the Patterson





School of Diplomacy and International Commerce, speculate that if terrorists were to target Kentucky, venues like Churchill Downs, Commonwealth Stadium and Rupp Arena would be on the list because they can hold more than 20,000 people.

While there is no immediate threat to the state, Tsuboi says a much more likely—and potentially devastating—target would be the hog and chicken industry in Western Kentucky. "If they infected chickens with a really nasty virus, all they'd have to do is wait for it to go through the normal chain of events."

As Tsuboi explains, the flu virus comes from China, which has a well-established pig and duck industry. Viruses naturally move from birds (ducks and chickens) to pigs to hu-

mans. "What's happening is the virus is maturing," he says. "The bird is a different living environment than a mammal (like a pig or a human). However, viruses can bypass the pigs and go directly from bird to human, and when they do they tend to be highly virulent."

"Plain old, garden-variety influenza can be very lethal because it mutates as it reproduces. That's why you have to get a flu shot every year—it's a different bug. Antibiotics are useless; you've got to have a vaccine. And you don't make vaccines overnight. In a good year we can whip up a vaccine in six months."

For years army and navy medical research units in Asia, Latin America, Africa, and Europe have monitored infectious

Douglas Scutchfield (left) and Martin Evans are developing bioterrorism drills for first responders: hospital and health department personnel, EMS, police, and firefighters.

diseases like influenza in order to identify the strain, allowing scientists time to manufacture vaccines to combat the specific bug before it makes its way to the United States. "But the world has shrunk and, despite 9/11, air travel is intense and our warning time is basically nonexistent," says Tsuboi.

### Spotlight on Public Health

One of the most important byproducts of last October's anthrax-by-mail attacks is an increased emphasis on public health.

"We've had a progressive erosion in the funding for the public health system over the last several years," says Douglas Scutchfield, director of the Kentucky School of Public Health. With new funds totaling \$15 million from the federal government, Kentucky will hire 15 new epidemiologists (a.k.a. disease detectives), assess how well its 123 hospitals are prepared to deal with bioterrorism, and upgrade animal laboratories in Lexington and Hopkinsville.

Part of this effort will involve table-top exercises, which Scutchfield and Martin Evans, medical director of hospital infection control at the UK Chandler Medical Center, say is the most effective way to train first responders for an outbreak. "A table-top exercise is a drill of an actual event," Scutchfield says. "It brings the relevant stakeholders together to demonstrate how the system would work in the event of an emergency and allows them to 'debug' their bioterrorism plans."

Unlike chemical or nuclear attacks where the first people on the scene will most likely be police, firefighters, EMS or FBI, the first responder to bioterrorism will probably be a doctor in an ER. "Identification is going to be very difficult because many of these diseases present with very common symptoms—fever, cough, diarrhea, rash—things we see all the time," Evans says.

"Most of us physicians have never seen a case of anthrax, much less smallpox," says Scutchfield. "We need to raise the level of knowledge about potential bioterrorism agents and how to recognize them, what to do, who you contact next, and how quickly."

Scutchfield and Evans envision rolling into a local hospital with a table-top exercise that would involve diagnosing and communicating information about specific bugs. "We'd involve all the agencies that are going to be mobilized in response to bioterrorism—the police chief, fire chief, health department director, mayor's office, EMS, and hospital personnel," Scutchfield says, adding that the Colorado public health department has already tried this.

"They had a mock smallpox outbreak, and it got to the point where the police and fire departments didn't answer their telephones because the system was overrun. That exercise illustrated that the cops couldn't communicate with the fire department, and neither of them could communicate with the public health department, without a specific communications plan involving cell phones and two-way radios. These exercises allow you to identify those kinds of issues in advance so you know how you're going to deal with them in the event of an actual emergency."

### Hospital Readiness

Evans, who leads the Bioterrorism Preparedness Task Force at UK, says this readiness effort is much larger than the University of Kentucky Hospital. "We gathered infectious-disease doctors and infection-control personnel from hospitals all over Lexington, and one of the very first things we had to decide was what we were going



to use to treat anthrax," Evans says.

While no anthrax cases were ever confirmed in Lexington, Evans says it was important to choose which drug all local hospitals would give out. Ciprofloxacin, the drug talked about most as the anthrax scare spread, is very costly—\$500 wholesale for a 60-day dose (120 tablets). Doxycycline, which comes as a generic—and subsequent tests have proven can be as effective as Cipro—is about \$6. "We didn't want to confuse the public by having disparity among the hospitals, where UK was giving the 'cheap' stuff and Central Baptist was giving the 'good' stuff. So we all decided to use Doxy."

Evans is working to prepare for bioterror scenarios in order to protect patients that come into the UK hospital, as well as UK's doctors, nurses and staff. "I don't anticipate major infection-spread problems with non-transmissible agents like anthrax and tularemia," Evans says. "The threat there is that somebody will expose others to the agent by coming in like Pig Pen, the character in the Peanuts comic strip, in a cloud of dust. Someone who suspects they've encountered those agents can simply put their clothes in a bag, shower down and put on fresh clothes before coming to the hospital."

"Pneumonic plague is a concern. You can cough out the bacteria and transmit it to other people, but it's fairly easy to give medications to protect health-care workers and isolate individuals because it's not the kind of thing that's carried by airflow patterns from room to room or floor to floor."

Smallpox, on the other hand, has the ability to spread

**The deadliest agents in bioterrorism are aerosols. These tiny particles can pass through the nasal passages and get deep into the lungs where they can cause disease. The Soviets successfully weaponized genetically altered, aerosol forms of anthrax, smallpox and plague.**

through a hospital via air ducts. "You'd need to put those patients in negative-pressure airflow rooms—we have quite a few right now for tuberculosis patients," Evans says. "The air comes from the hallways into the rooms and then is exhausted to the outside, generally from the roof. That's sufficient for TB because the bacteria are diluted by the huge quantities of air outside. But the CDC doesn't really feel the same about smallpox. They'd like us to have HEPA filters on the exhaust." These filters are expensive, and Evans says a better care alternative for smallpox patients would be designating and equipping one hospital to handle all smallpox cases in the region.

## **Smallpox, the "King of Bioterrorism"**

The United States stopped mandatory vaccination against smallpox in 1972. "The world was declared free of indigenous smallpox in 1980, and it was thought at the time—naively—that smallpox would be eradicated," says Richard Greenberg, a professor of infectious diseases who is leading the first clinical trial of a new smallpox vaccine at UK.

"The Vector Institute in Russia was creating barrels of smallpox at the same time eradication efforts were being conducted by such famous people as D.A. Henderson, head of the World Health Organization (WHO) global vaccination effort."

"Smallpox is the king of bioterrorism," Greenberg says. "It's the ideal agent in that it's highly contagious. It could easily incapacitate an army."

In 1974 he spent three months with the WHO in Bihar, India, vaccinating people against smallpox. For hundreds of years in that country, small groups of people actually worshipped the virus. "They would take their children and infect them (a religious rite called variolation). They thought that if you gave children a small amount of the virus, they would survive the infection and be blessed by the god of smallpox," Greenburg says. "They would harbor someone with smallpox and not report them for fear that the community would be vaccinated and people would not have a chance to be variolated."

"Of course some of the people who were variolated died. And there have been outbreaks of particularly virulent strains of smallpox in India where over 90 percent of the people have died." On average, 30 percent of people who contract smallpox die, and if you visit India today the ravages of smallpox are



Richard Greenberg, head of UK's clinical smallpox trial, sits in front of an image of vaccinia, the virus used in the smallpox vaccine.



Vaccinia virus © Scott Camazine/www.osf.uk.com

still visible on the faces of many people in their 50s and 60s—they bear the unmistakable pitted scars.

Twelve days after exposure to the virus, patients have sudden onset of fever, headaches, backaches, vomiting and even delirium. Two days later the smallpox rash appears on the face and extremities. It begins as tiny pink spots, which enlarge into pustules (or pocks) filled with fluid. The pocks dry up and scab off, leaving sunken scars. The scabs themselves are just as contagious as the pocks. There is no effective antiviral medicine to treat smallpox; all doctors can do is give supportive care: IV fluids and antibiotics for secondary bacterial infections.

Recent articles in *JAMA*, the journal of the American Medical Association, say that if you are immunized within five days of exposure to smallpox, you won't die.

"The data is pretty soft," Greenberg says. "At the time of a mass outbreak, this may not be the case. You might not be killed, but you're going to be debilitated. Not many people

**"Since 9/11 everybody has felt a little smaller, a little weaker, and a little bit more vulnerable to the crazy people on Earth. This is our way to contribute."**

—Richard Greenberg



can go to work with a 104-degree temperature and sores all over their skin."

"As a physician and epidemiologist, I personally have a problem with telling the people who work in the ER: 'Go ahead and take care of this patient. The CDC will be here within five days to give you your immunization, and you'll be okay,'" Evans says. "Mass vaccination is being debated now on the national level because 200 million doses of vaccine should be available by the end of the year."

These doses are diluted versions of the old vaccine, which Greenberg says is no longer FDA-approved because some of its ingredients have expired and because it was originally grown on the bellies of cows (a practice now condemned since the advent of mad cow disease). Greenberg also says they're probably "cutting it close" because scientists aren't sure just how much virus you need in each dose for the vaccine to still be effective.

In June 2002, the Advisory Committee on Immunization Practices, which sets U.S. vaccine policy, recommended against vaccinating all Americans against smallpox. The committee plan calls for states to designate smallpox response teams—doctors, epidemiologists, nurses, lab workers, and law enforcement officers—who would receive the vaccine. Despite criticism, this decision rings true with the known risks.

The vaccine can, on a rare occasion, cause severe rashes, brain swelling and death in infants or in people with skin disorders (like eczema or psoriasis), HIV/AIDS or who are immunocompromised. Experts estimate that 300 people would

die from side effects if the whole nation were vaccinated.

You can't get smallpox from the vaccine, because it's made from a weakened virus called vaccinia (a distant relative of variola, the virus that causes smallpox), but people whose own defenses can't contain it can have adverse reactions. "We give VIG (vaccinia immune globulin) to kill the vaccinia virus in vaccinated people with immune-compromised conditions—HIV, cancer, organ transplants—or who have it spread to an area of skin that can't defend itself," Greenberg says.

"We know what the side effects are. We have almost two centuries' worth of data on what kind of people won't do well if they get vaccinated. Those people shouldn't be involved in clinical research and we screen them out.

"It's important for people who get vaccinated to protect the vaccination site not only from the elements, but from their hands and other people until the scab has fallen off," he says. "This doesn't mean hospital staff can't go back to work after being vaccinated; they just need to take precautions."

### UK's Smallpox Trial

A detailed list of these precautions was included in the 16-page consent form the 150 volunteers had to sign to join the smallpox vaccine trial. UK is the exclusive site for this clinical trial and was chosen, according to Terry Irgens, president of DynPort Vaccine Company in Virginia, because of the university's excellent reputation and Greenberg's expertise.

Claire Pomeroy, chief of the Division of Infectious Diseases and associate

chief of staff at the Chandler Medical Center, says, "Dr. Greenberg's team has a long track record of doing vaccine studies, and those skills are being brought to bear on this challenge." Greenberg, who conducted his first trial in 1978, has conducted clinical trials at UK since 1989. He currently has two other vaccine trials under way for the prevention of shingles and HIV.

"About a year ago DynPort, the vaccine contractor for the military, wanted to know if anyone in the country was willing to do trials of their new smallpox product to get FDA approval," Greenberg says. "They visited us last summer, and we helped them write the protocols for the study.

"This is probably as important a project as I've ever tackled. Since 9/11 everybody has felt a little smaller, a little weaker, and a little bit more vulnerable to the crazy people on Earth. This is our way to contribute."

Beth Plummer, a clinical researcher at UK since 1989 and Greenberg's "right-hand" in this project, says this is a unique opportunity for Kentuckians. "This is clinical research where the volunteers can gain a tangible benefit from participating—immunity against smallpox. Plus they are contributing to medical knowledge that can get this vaccine approved."

"This study is moving the national agenda forward," Pomeroy says. "No one can take the next step, deciding whether we should vaccinate the nation, until we have proven that we have a safe vaccine to offer people. We need to have these answers. The national spotlight is on Kentucky."

This trial, designed to compare the



Smallpox vaccination: a small drop of the vaccine is applied on your upper arm, and 15 needle pricks (with a bifurcated needle like the one pictured) are made into the drop to transfer the vaccine into the skin.



safety and effectiveness of DynPort's new smallpox vaccine (CCSV) to the existing smallpox vaccine (Dryvax), enrolled 150 healthy, previously unvaccinated volunteers between the ages of 18 and 30. Fifty volunteers were randomly selected to receive the existing smallpox vaccine; the remaining 100 received the new vaccine. All volunteers were followed for 180 days, and a group of 60 volunteers will be followed for three years. Volunteers' blood will be tested for antibodies specific to smallpox at various points throughout the study.

"This is the first time we've followed people to study how long the smallpox vaccination lasts," Greenberg says. Experts estimate that the immunity provided by the old vaccine may last up to 10 years. "We know that if you take cells out of people who've been vaccinated 50 years earlier, they still have a response to the antigens in the test tube, but we don't know how vigorous that response is."

Greenberg says they'll probably have to do two additional clinical trials, involving 4,000 more people, before FDA approval. The next trial will have much looser criteria: people ages three through 75.

What makes this vaccine new is technology: this product is grown in a laboratory versus being grown on the skin of cattle or sheep.

"The vaccinia virus used in the new vaccine originally came from camels and water buffalos. It has been used for human vaccination since the late 1920s," Greenberg says. "The virus is cultivated and harvested from layers of cells using Nunc™ cell factories." The result: a "cleaner" vaccine with fewer animal byproducts.

DynPort is working on this vaccine for the U.S. military, and the federal government selected Acambis Corporation in Massachusetts as its contractor for vaccines for the civilian population.

"Our main challenge in recruiting for this trial was educating 18- to 30-year-olds about the importance of this study," Plummer says.

"There is definitely a generation gap between people over 30 and under 30," Greenberg says. "This younger group has no connection with smallpox—grew up in an era with no TV coverage of epidemics—and has no idea what it is."

He says the benefits of developing this vaccine are twofold: it's an obvious deterrent against bioterrorism, and, if more people are vaccinated, it will be easier to manage an outbreak if it happens.

"Smallpox is the ideal weapon to hold this country hostage," Greenberg says. "If we go into a country harboring terrorists, that country could threaten to release smallpox if we invade. Then who would be the bad guy?"

**A recent list, made by the U.S. government, of organizations suspected to have or of trying to obtain smallpox reportedly includes China, Cuba, India, Iran, Iraq, Israel, North Korea, Pakistan, Russia, and Serbia, as well as the terrorist group of Osama bin Laden and the Aum Shinrikyo sect in Japan.**



Bubonic plague expert Susan Straley (left) has 11 people on her research team, including Tanya Myers, a research analyst who has worked with Straley for three years.



## The New Threat of Plague

Susan Straley isn't a bioweapons expert. But she's well aware of the noxious potential of *Yersinia pestis*, the bacterium she's studied since 1979.

"Inhaling as few as 100 of these bacteria can cause pneumonic plague," says Straley, a professor of microbiology and immunology who came to UK in 1983. Given the fact that scientists estimate each square centimeter of our skin teams with an average of 100,000 bacteria, these 100 bugs pack an extraordinary punch.

"As little as one day after inhalation you start showing severe symptoms of pneumonia, and the next day you could be dead," she says, adding that's a very narrow window for correct diagnosis and treatment.

What's even more frightening is that although researchers have been studying *Yersinia pestis* for more than 100 years, very little is known about pneumonic plague. Most of what they've learned focuses on bubonic plague, the much more common form of the disease spread by infected fleas. Bubonic plague killed 25 million people in Medieval Europe and continues to kill up to 2,000 people worldwide each year.

The bioterrorism potential of an aerosol release, and the inevitable social turmoil that would result from a pneumonic plague outbreak, landed plague on the CDC's bioagent hit list. This is why Straley has begun to apply everything she knows about the spread of bubonic plague to the rarer pneumonic form.

She describes the route of infection for bubonic plague: "Pretty early after the bugs are injected into a mammal, they



will come into contact with host cells. And they are thought to enter some of those cells, particularly our innate defense cells called macrophages." Before the immune system has a chance to gear up, macrophages serve as a safe haven for *Yersinia pestis* to start manufacturing a special delivery system for their toxins.

Meanwhile, PMNs (polymorphonuclear neutrophils), the body's own "bug terminators," are activated by the immune system. PMNs do battle with the bugs, but the bugs have the upper hand because, Straley explains, as they multiply they turn on properties that prevent them from being destroyed by the PMNs.

"Now the bugs get into lymph, the fluid in your tissues circulated by the lymph system. It's like a series of open culverts. The bacteria enter the lymph tubes and are collected and filtered by lymph nodes. There are lots of PMNs and macrophages waiting in the nodes, and the battle continues." The chemical signals from this battle set off a huge inflammatory response: more cells come in to join the fight. The result—a swollen lymph node called a bubo. "The time from infection to bubo is about five to seven days," she says.

The lymph carries the bacteria into the blood, and from there they attack the blood-filtration organs, the spleen and liver. More PMNs

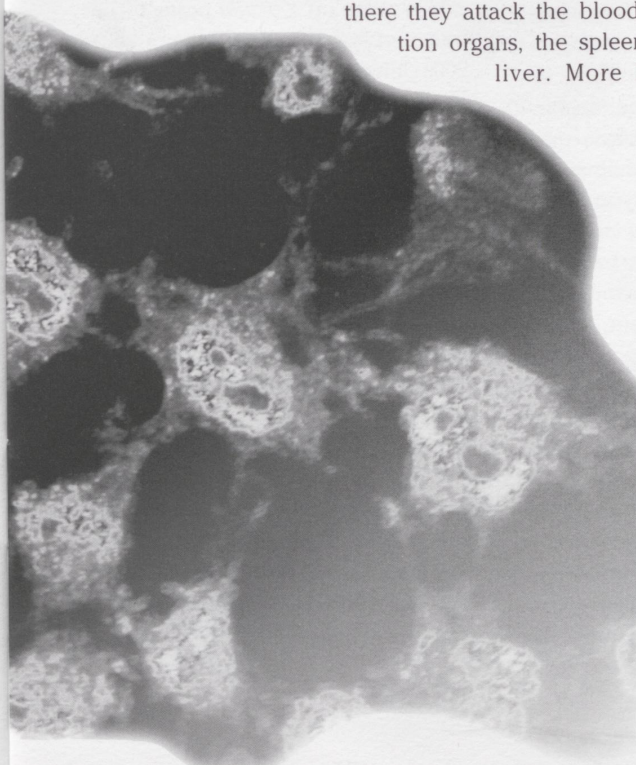
and macrophages in those organs fight the infection. "Some of the bugs are killed for sure," says Straley, "but the bacterial numbers just overwhelm the immune system and bugs go everywhere."

"They wind up in the lungs, and in the terminal stages of bubonic plague you can develop pneumonic plague." In this contagious and highly dangerous stage, coughing can spread the disease from person to person.

In the case of direct pneumonic plague infection (which occurs in less than 14 percent of naturally occurring plague cases), the inhaled bugs have already adapted to the body of the first person, so they arrive fully armed with their toxin-delivery mechanism. Straley says this gives the bacteria a head start in the race against the body's defenses. As in bubonic plague, the bacteria first encounter macrophages—in this case alveolar macrophages, the lung's defense cells. "Some of the bacteria go into macrophages, you get an influx of PMNs and then inflammation. Part of inflammation is fluid influx, so your lungs fill up and you can't breathe," says Straley. "The bacteria also spread to the lymph nodes and the blood, so the basic process is the same as in bubonic plague, but we really know very little about the specifics."

One of the major areas of Straley's research grew out of the overarching question: "Why are these bugs so virulent?" She says their incredible capacity for causing disease has to do with a specialized delivery mechanism for toxins that looks remarkably like a pushpin you'd stick into a bulletin board.

"This pushpin is a molecular machine," she says. "The machine has maybe 21 parts—some of them moving parts. The bugs assemble these to get their toxins into cells."



This image shows the distribution of the protein YopM in cells four hours after infection. The whitest areas show the highest concentration of YopM. The strands that stick out are *Yersinia pestis*, the bacteria that cause plague.



**During WWII, the Japanese created bombs (a porcelain shell filled with cotton, wheat, rice, and live fleas infected with bubonic plague) that killed hundreds of Chinese.**

This pushpin machine's official name is the Type III Secretion System. "UK participated in its discovery," Straley says. "A number of other human pathogens have this system—*Salmonella*, *Shigella*, *Chlamydia*, *E. coli* 0157:H7. Right now many scientists and drug companies are actively working on ways to target this system."

"When the needle—the part that sticks out—comes in contact with a host cell, it punctures the cell and samples the cytoplasm [the cell's internal fluid]. In response to the low calcium environment inside the cell, the bug's secretion mechanism is activated, and it sends toxins right into the host cytoplasm."

These toxins are called Yops, which stands for *Yersinia* outer proteins. "These Yops mimic key cell biological reactions and modify them in a way that is advantageous to the bacteria," Straley says. Six Yops have been identified, and she says there are probably more. "One of the bug's early high-priority activities is to prevent being engulfed and destroyed by macrophages and PMNs; three of these Yops participate in that."

Of the six Yops that have been identified, one is still an enigma—YopM. "This Yop gets delivered to the cytoplasm just like all the others, but for some reason it hitches a ride with the

cellular trafficking system and winds up entering the cell nucleus. If we can identify what YopM does inside the nucleus, it may shed light on why these bugs are so virulent."

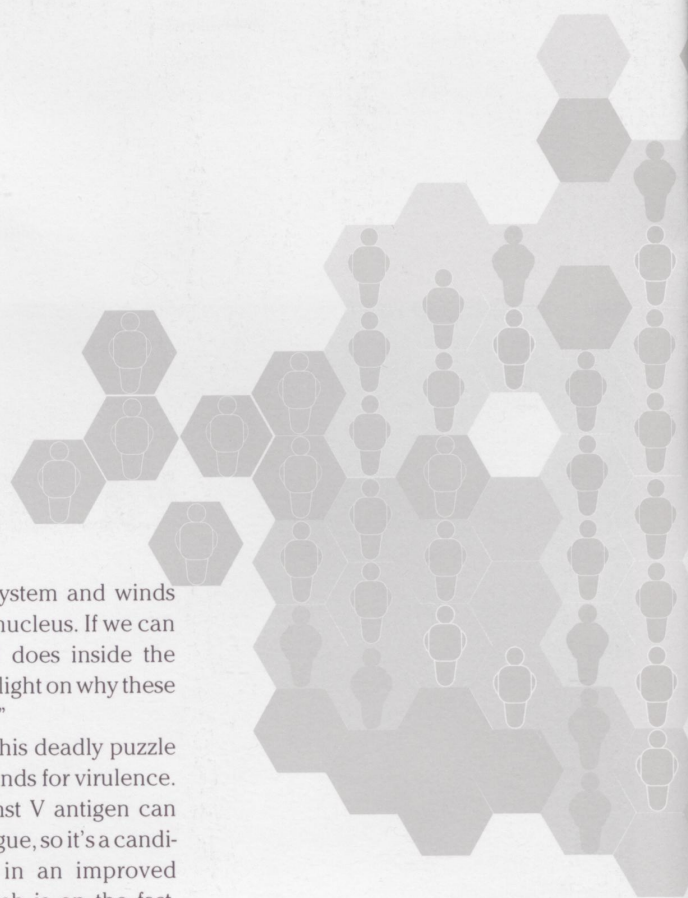
Another piece in this deadly puzzle is V antigen—"V" stands for virulence. "The antibody against V antigen can protect you from plague, so it's a candidate for inclusion in an improved plague vaccine which is on the fast-track," Straley says. (There is no longer a licensed plague vaccine in the United States.) "Unfortunately, we don't know fully how V works. It does multiple things, which is the problem."

Straley explains that V antigen, in some way, regulates the gate mechanism that activates the pushpin machinery. It also sponsors the delivery of Yops. "If you don't have V, you don't have Yops delivery." And V antigen, Houdini-like, gets outside the bacteria all by itself—sometimes it goes out with the Yops through the pushpin, sometimes it doesn't.

"We know V antigen down-regulates the immune system," she says. When the immune system activates, it's incredibly potent. It has built-in regulators that stop it when the infectious insult is over and return things to normal. "Well, V makes this happen early, which is one of the reasons these bugs multiply so rapidly."

Straley's primary UK partner in plague research is colleague Robert Perry, whose work on *Yersinia pestis*'s iron-transport systems earned him a 2001-2002 University Research Professorship [see [www.rgs.uky.edu/ca/odyssey/fall01/researchprofessors.html](http://www.rgs.uky.edu/ca/odyssey/fall01/researchprofessors.html)]. Straley and Perry are collaborating on a project focusing on the development of pneumonic plague that's getting down to the nitty-gritty of how the bacteria adhere to the lungs.

"One of the first things that happens in any infection is the bugs attach to something. We want to identify what they are using to adhere, with the idea that if we could identify the molecules involved, we could make therapies to counteract those molecules. So some kind of vaccine or drug that would be effective early in pneumonic plague could prevent the infection from happening."





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Fighting pathogens in the field:  
(left to right) Thomas Kemp  
(horticulture professor),  
Katherine Akers (research analyst),  
Melissa Newman (animal  
sciences assistant professor) and  
Randy Collins (research analyst)

## Bioterrorism and Your Food

"Tragically, terrorists are very inventive," says Claire Pomeroy, chief of infectious diseases at UK, as she talks about an unsuccessful, but eye-opening, domestic bioterrorism attack.

In September 1984, a 10,000-member cult led by Bhagwan Shree Rajneesh used *Salmonella* to contaminate salad dressing and coffee creamers at 10 restaurants in the Oregon town of The Dalles. Their goal: change the outcome of the November election for county commissioner by food-poisoning voters. At least 751 people became sick. "They didn't succeed in affecting the election, but this attack made it clear that this kind of thing is within the realm of possibility. These cult members had no special training," Pomeroy adds.

"With bioterrorism, they don't really need to succeed—all they need to do is put doubt in people's minds," says Melissa Newman, a microbiologist specializing in food safety and animal nutrition in the UK College of Agriculture.

*Salmonella*, the number one food-borne pathogen, tops UK scientists' list of most-studied bacteria, a list that also includes *E. coli*, *Shigella*, *Listeria*, and *Staphylococcus aureus*.

"Not all bacteria on food are harmful," says Newman, who came to UK five years ago from a microbiology company in

Cincinnati. "You have a natural population of bacteria that sit on the surface of fruits and vegetables and that are benign."

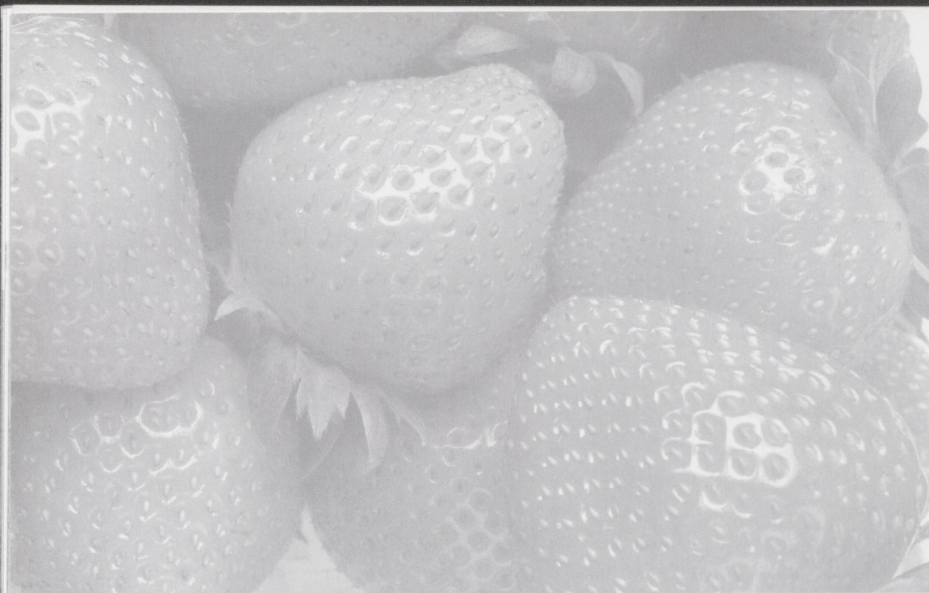
Food-borne pathogens can taint fruits and veggies at a variety of stages in production. It can happen in the field (spread by animals or contaminated irrigation lines), and it can happen at harvest (with poor-quality rinse water). It can happen in transport (refrigerated trucks or railcars that are dirty or contaminated by the last thing they hauled). And it can happen in your kitchen.

"Most food-borne illness occurs at home as a result of cross-contamination. Mom cuts up the chicken and the tomatoes on the same cutting board," Newman says. Besides eliminating cross-contamination, the best way to protect your family is by refrigerating and then thoroughly washing fruits and vegetables.

"Most people think products like Fit [a shampoo for fruits and veggies] were put on the market to get rid of bacteria. But most of those products are designed to rinse off pesticides," Newman says. "The washing process itself takes care of most of the bacteria."

While not common, there have been several food-borne bacterial outbreaks. "Awhile back we had problems with *E. coli* 0157:H7 in unpasteurized apple juice and cider," Newman





says. The problem with this bug is its acid tolerance—the natural acids in apples don't inhibit the bacteria's growth. "This *E. coli* is naturally found in cows, but it's not harmful to them because they don't have the same intestinal structure as humans," she says. "It's a fascinating organism because it's the poster-child of bacterial survival. The sad part is it targets infants and young children with inexperienced immune systems." *E. coli* 0157:H7 can cause irreversible damage to the kidneys resulting in death.

After the *E. coli* 0157:H7 outbreak, orchards made new rules. One, no picking apples off the ground. "If they're on the ground, they're bruised and the pathogen can get inside," Newman says. Two, no fertilizing with fresh manure. "In some cases orchards were running cows through, so the manure was *really* fresh," she says. "The cows would eat the apples on the ground and then deposit their own apples."

*E. coli* has also caused problems in sprouts. Contaminated radish sprouts caused an outbreak in Japanese school children, and alfalfa sprouts, grown in the United States, have been plagued by the bug. Newman is using natural compounds from strawberries—"components of the strawberry odor and flavor"—to fumigate sprout seeds to prevent bacteria from growing.

Before Newman came to UK, Thomas Kemp and Doug Archbold, in the horticulture department, had been looking at the ability of these natural compounds to deter mold growth on strawberries. "I wondered what would happen to pathogens on sprout seeds treated with the compounds," she says. It turns out this approach has been pretty effective at killing *Salmonella* and *E. coli*, and the treatment doesn't affect the speed of germination. Newman is also looking at fumigating the sprouts themselves.

Kemp says these compounds, known as natural plant volatiles, are vapors given off by most plants. "These compounds are the aroma you detect when you eat them," he says. Kemp, Archbold and Newman are partners on a project to detect pathogenic vapors by "sniffing" the air around produce with a special device called a solid-phase microextractor.

"It's a syringe with a hollow, half-inch-long glass tube inside the needle. The tube walls are coated with liquid that will soak up any vapors in the air," Kemp explains. "We then flash-heat the vapors off (at about 200 degrees Celsius) into an instrument called a gas chromatograph that separates out all the components." This technology, developed in the early '90s, was created by the EPA to look for pollutants

in the air. "It works quite well for this too," Kemp says.

The beauty of this process is that it's nondestructive—the air around the fruit is sampled, not the fruit itself.

Kemp's hope was to find markers—distinct sets of chemicals—given off by pathogens growing on fruits, veggies or meats. "We found that the markers for the vapors bacteria make are very different from what plants make. Bacteria make a special type of alcohol that our instrument can detect.

"Melissa and I have talked about a handheld device, sort of like a breathalyzer, for consumer use that could detect what's in the air around produce. It's not unrealistic to think you might have something like that in your kitchen in the future.

"Our food supply sources have changed," Kemp says. "More and more produce is coming from other countries, and what is grown here is produced on huge farms."

Newman says these large food-processing companies are well aware of bacterial, as well as bioterrorism, risks.

"I think the threat of bioterrorism is more attractive to would-be terrorists than actually going through with an attack," she says. "Most of these bacterial agents won't give them the end product—high fatalities—they want; they'll just incapacitate people for a short time."

She cites *Staphylococcus aureus* as an example. "Most of us carry it on our skin, but under the right conditions it can produce a heat-stable toxin. If this toxin were in your food, it would make you sick to your stomach for four to six hours."



## Antibiotic Resistance: The Real Threat

Newman's main passion is antibiotic resistance. "We get caught up in talking about antibiotic-resistant bacteria. It's not bacteria in and of themselves that's really the issue—it's the genetic material they transport." She explains that bacteria share genetic material—they copy plasmids (extra pieces of DNA) and hand out copies to their neighbors. These copies can include resistance to one or many antibiotics, and bacteria aren't xenophobic about sharing this information. "Genetic material can be transferred from this *E. coli* to that *E. coli* to a *Salmonella*," she says. "This material can come from nature, and it can come from human use."

Newman says while antibiotic resistance is natural (microorganisms naturally arm themselves with antibiotics to compete for nutrients), humans are exacerbating the resistance. "Doctors who prescribe antibiotics to treat the flu contribute to it, since the flu is caused by a virus, not bacteria. Individuals who use antimicrobial hand washes contribute to it—the mode of action of those hand washes is very similar to the action of many antibiotics."

"You sometimes hear people say the problem with our health today is that we don't eat enough dirt as a child. In some ways that's true." She says the widespread use of antibacterial cleaners and washes is basically promoting a bacterial population that can survive these chemicals.

Newman says the farm also plays a role in antibiotic resistance. Antibiotics are used on the farm primarily to prevent illness in healthy livestock and to speed up growth to increase production. "We need to focus on conservative use of antibiotics," she says. Europe has banned the use of almost all antibiotics in animals. In the United States, the Alliance for Prudent Use of Antibiotics recently recommended we stop using antibiotics for increased production, but allowed use to treat illness.

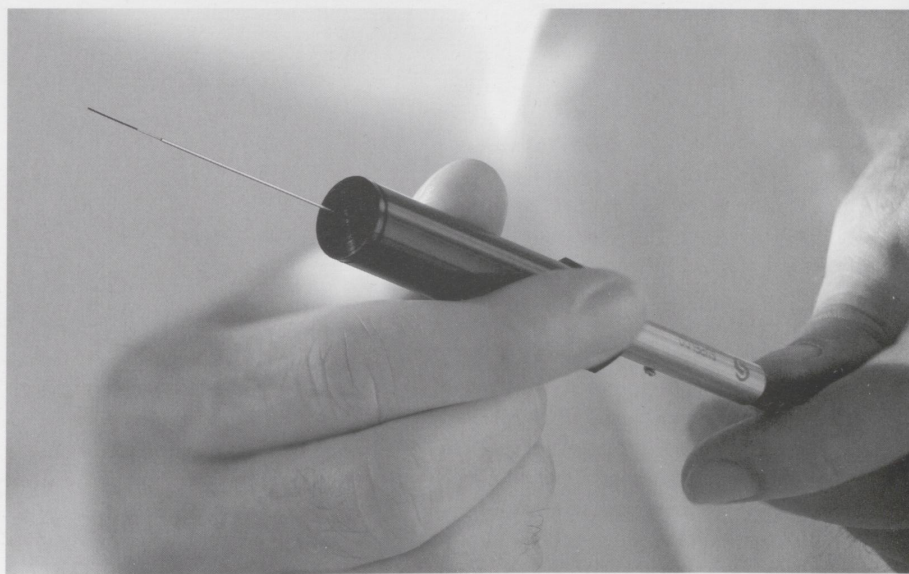
"The number of people who die from antibiotic-resistant bacteria is unclear," Newman says. "There has been some sensationalization, but we need to act now to get out in front of this. There are natural alternatives to antibiotics, and certainly big companies realize this."

Tyson's has reduced or eliminated antibiotic use in its poultry, a fact the company touts in its advertising. "For a long time people have said, 'If we stop using antibiotics, resistance will go away.'"

But Newman says that's not true, as evidenced by the herd of pigs the College of Agriculture has in Princeton, Kentucky. "These animals have not received any antibiotics for almost 30 years, and still significant amounts of antibiotic resistance can be detected. This research has provided a great deal of evidence that things like heavy metals in the environment, fertilizers and sanitizers encourage bacteria to hang onto antibiotic resistance."

She says, "Resistance is something we have to address because antibiotics are the key to all modern medicine." ■

A solid-phase microextractor, the device that "sniffs" the air around produce to detect pathogens



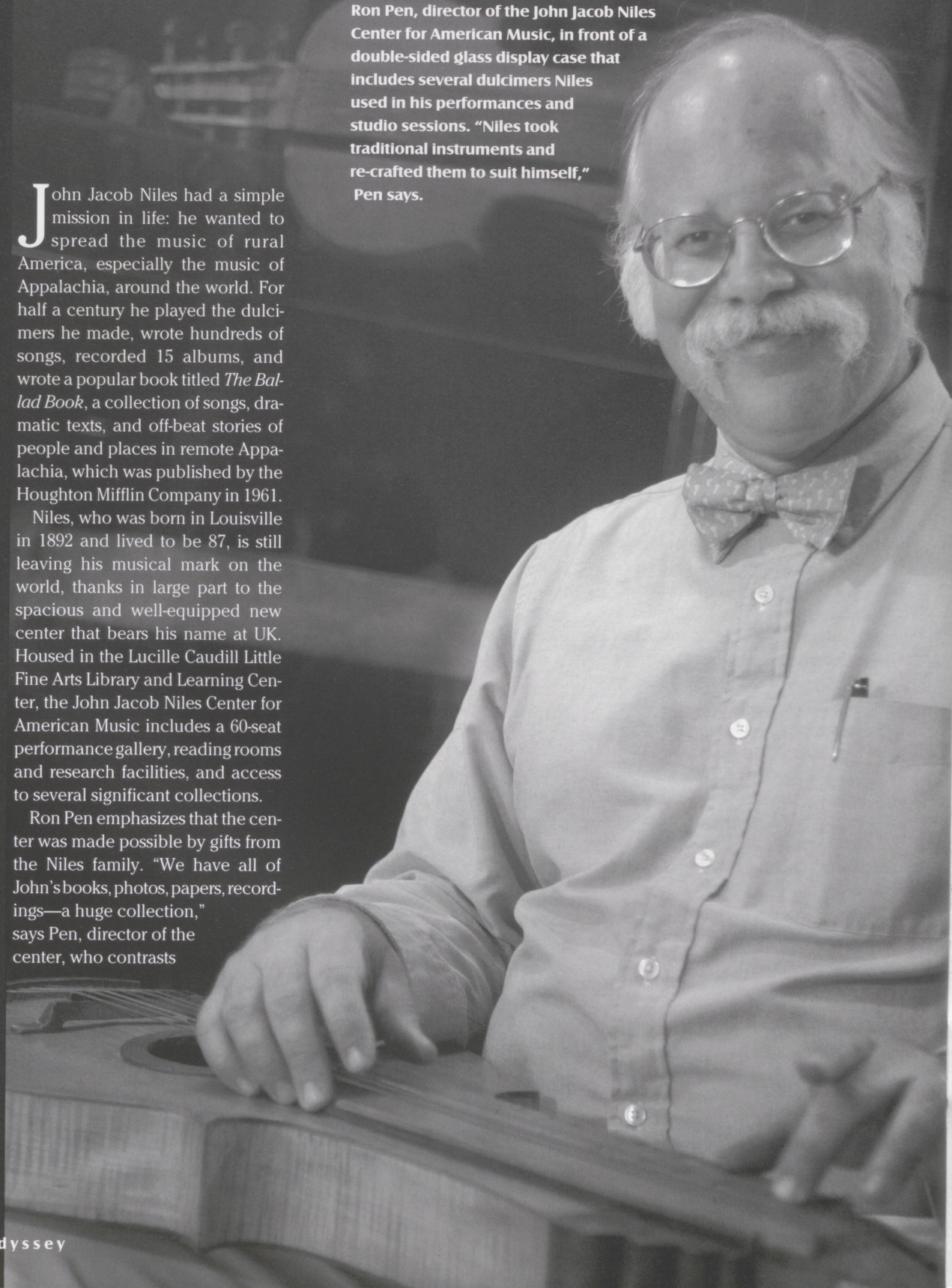


**J**ohn Jacob Niles had a simple mission in life: he wanted to spread the music of rural America, especially the music of Appalachia, around the world. For half a century he played the dulcimers he made, wrote hundreds of songs, recorded 15 albums, and wrote a popular book titled *The Ballad Book*, a collection of songs, dramatic texts, and off-beat stories of people and places in remote Appalachia, which was published by the Houghton Mifflin Company in 1961.

Niles, who was born in Louisville in 1892 and lived to be 87, is still leaving his musical mark on the world, thanks in large part to the spacious and well-equipped new center that bears his name at UK. Housed in the Lucille Caudill Little Fine Arts Library and Learning Center, the John Jacob Niles Center for American Music includes a 60-seat performance gallery, reading rooms and research facilities, and access to several significant collections.

Ron Pen emphasizes that the center was made possible by gifts from the Niles family. "We have all of John's books, photos, papers, recordings—a huge collection," says Pen, director of the center, who contrasts

Ron Pen, director of the John Jacob Niles Center for American Music, in front of a double-sided glass display case that includes several dulcimers Niles used in his performances and studio sessions. "Niles took traditional instruments and re-crafted them to suit himself," Pen says.





# John Jacob Niles Has a New Kentucky Home

W R I T T E N   B Y  
J e f f   W o r l e y

this new location with what passed for a "center" in previous times. "Before, the John Jacob Niles Center could be found only in my cluttered UK office and in my head."

An impressive double-sided glass case greets UK students, faculty, staff, and visitors to the center. This display includes several dulcimers Niles used in his performances and studio sessions—including some he made himself—and other folk instruments that he made for his own use. "Niles took traditional instruments and re-crafted them to suit himself," Pen says, an adaptation that accounts for a couple of the hybrid instruments on display: a "cello-influenced" dulcimer and a lute-like dulcimer.

Niles wrote some of the most widely played songs in America, specializing in the ballad: "Black Is the Color," "Go 'Way from My Window," "I Wonder as I Wander," and "Jesus, Jesus, Rest Your Head."

Pen explains that while the focus of the center is on Niles and his various musical contributions, the center's mission is to facilitate research and performance of the whole range of American music, from unpolished grassroots front-porch picking to more cultivated musicianship. "We do have a special emphasis on the musical culture of the southeastern United States," Pen says, "but we have materials here that date from Colonial times to the present."

One of the center's most impressive collections is of American hymnals, from Helen and Glenn Wilcox in Western Kentucky. "This is one of the largest collections of American hymnology

in the country," Pen says. "We purchased it when the Niles Center was first being developed, and it's an absolute gold mine of reference material—about 5,000 books." Pen adds that the rarest and most valuable book in the collection is the *Bay Song Book*, a collection of hymns sung by the Massachusetts Bay colonists and the first book ever published in America. "Some people say this book is more valuable than the Gutenberg Bible because it's more rare," he says. Pen is quick to point out that the center's copy is not a first edition.

Pen was the natural choice as director of the center. He has had a lifelong interest in folk music, and he wrote the foreword to the republication of *The Ballad Book of John Jacob Niles*, out of print for many years, and shepherded it through production. This edition was published in 2000 by the University Press of Kentucky.

"One of my earliest musical memories was singing a folk song, which turned out to be a Kentucky folk song, in public," Pen recalls. "I was seven, I think, and was somehow chosen to be in a chorus at the Lyric Opera House in Chicago. A group called the Limelighters was recording a song and wanted to be backed by a group of children." The song was "The Riddle Song" ("I gave my love a cherry, that had no stone/ I gave my love a chicken that had no bone") and it made a lasting impression on Pen. "I absolutely fell in love with it. The melody could make me cry!"

He had already been taking piano lessons since the age of four, so he admits he had a jump-start on acquiring an appreciation for music. But Pen

confesses he agreed to take piano lessons only because of the alternative. "My mother said it was either that, or I had to take a nap," Pen says, "and of course no self-respecting kid wants to take a nap."

He took piano lessons with the same teacher for 14 years and also along the way picked up the guitar.

"This was just something I wanted to do," he says. "A few years later, I found myself playing in a band called Cartoone House, which was the name of the house where I lived at the time with some college buddies. We played around some, including at the Washington Monument in an anti-war rally in the '60s."

Pen's strongest musical desire was to be a composer, so he familiarized himself with all the classical instruments and was a composition major at Washington & Lee University in Virginia. "But then when I got to UK, Don Ivey suggested that I should be a musicologist, not a composer. Well," Pen laughs, "I've become a music historian, which is pretty much the same thing."

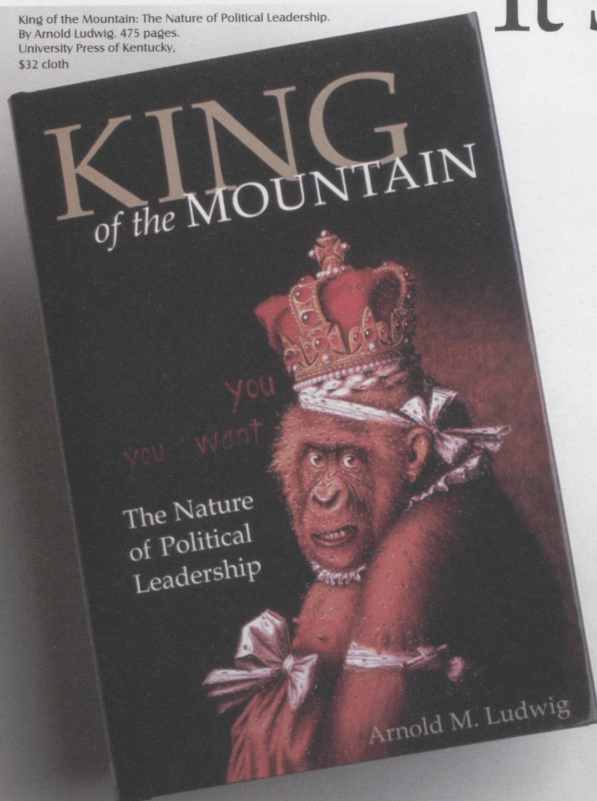
He came to UK in 1983 and earned a Ph.D. in musicology in 1987. Pen joined the faculty here four years later.

"It's been wonderful to watch our School of Music grow these last 20 years. 'We're much more vibrant now; musically, we've become a national institution.'"

And it's clear Pen is enjoying his role in the John Jacob Niles Center. "What we honor at this American music center is the music that's closest to home. This is the music that has the greatest power to affect us, and to nurture the community." ■



King of the Mountain: The Nature of Political Leadership.  
By Arnold Ludwig. 475 pages.  
University Press of Kentucky,  
\$32 cloth



**"What an ugly beast is the ape, and how like us."  
—Cicero (106-43 B.C.)**

World leaders, it turns out, are engaged in a lot of monkey business.

In *King of the Mountain*, Arnold Ludwig's 10<sup>th</sup> book, the author profiles 1,941 rulers from 199 countries. One of the discoveries he made along the way was that political leaders tend to display the same characteristics as simian alpha males.

"As I got into this project, more and more questions began to present themselves. Why were these people so intent on vying for the top position? Why were they willing to suffer so much—jails, beatings and even exile—to get and hold on to this position?" Ludwig's search for answers led him to reexamine the writings of Jane Goodall and other specialists in primate research.

"Male chimps have to test themselves in order to become the alpha male," says Ludwig, emeritus professor of psychiatry at the University of Kentucky. "But if they ascend to this position, they get all sorts of privileges—more females, better food and shelter, and an army of deferential followers." He adds that there is clearly a downside to all this. The alpha male must be willing to do almost anything to keep this position. "Once they gain ultimate power, they are at great personal risk. Between 12 to 18

# It's Good to Be KING

percent of the rulers I researched died violent deaths by assassination, execution or suicide as a result of being in office."

Alpha male behavior is extremely visible, he points out, in recent American politics: former Vice President Gore's reputed lessons on how to act like an alpha male during the presidential debates, the appeal of Senator McCain as an American war hero, former President Clinton's unrestrained sexual appetite, and President Bush becoming "more presidential" since 9/11.

Ludwig admits that characterizing every ruler of a recognized nation in the 20<sup>th</sup> century was a massive undertaking.

One of the impressive features of the study, which took 18 years to complete, is that from the larger group of rulers, 377 were looked at in detail. "In this excerpted group, I looked at religious upbringing, education level completed, method used to rise to power, how their rule ended, and the cause of their death, among other things," he says. One interesting outgrowth of this, he says, is the Political Greatness Scale that he created.

"I was wondering how I might do such a thing, when suddenly it hit me: I could take a look at who society regards as the greatest rulers of all time and use their challenges and accomplishments as a touchstone. I came up with 26 names, pre-20<sup>th</sup> century—Napoleon, Louis XIV, Bismarck, Moses, Genghis Khan, and others—and found certain common traits I could use to rate the achievements of 20<sup>th</sup>-century leaders."

Ludwig's research revealed an overwhelming gender discrepancy. In the larger group of nearly 2,000 rulers, 98.6 percent were male. He also found it "simply horrifying" that in the 20<sup>th</sup> century rulers contributed to over 200 million deaths from wars and oppressive social policies.

"And I happen to believe that these two things are connected," Ludwig says. "Underlying these deaths is the strong biological component of the leaders—almost all male—and unless we address this, all other efforts at peace may be futile. At no point have we taken into consideration that our problems with killing each other may be related to our struggles for dominance."

Ludwig believes one way to reverse the numbers of deaths from wars might be to adopt more of an "estrogenic approach" to ruling. "There not only should be far higher percentages of women in power, but they should be well represented at every level: cabinet posts, ambassadorships, and the highest military ranks. I believe that countries then might not be so confrontational."

—Jeff Worley



Odyssey  
Fall 2002

# Parting Shots

"Things have never been more like the way they are today in history."

—Dwight Eisenhower

"In America, anyone can become president. That's one of the risks you take."

—Adlai Stevenson

"When we got into office, the thing that surprised me the most was that things were as bad as we'd been saying they were."

—John F. Kennedy

*"It's our fault. We should have given him better parts."*

—Jack Warner on hearing that Ronald Reagan had been elected governor of California

"There is no distinctly American criminal class—except Congress."

—Mark Twain

"It's no exaggeration to say that the undecideds could go one way or another."

—George Bush

"I am not worried about the deficit. It is big enough to take care of itself."

—Ronald Reagan

"There they are. See no evil, hear no evil, and...evil."

—Bob Dole, watching former presidents Carter, Ford and Nixon standing by each other at a White House event



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