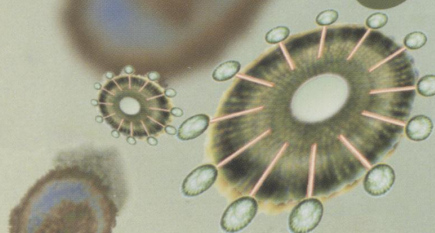
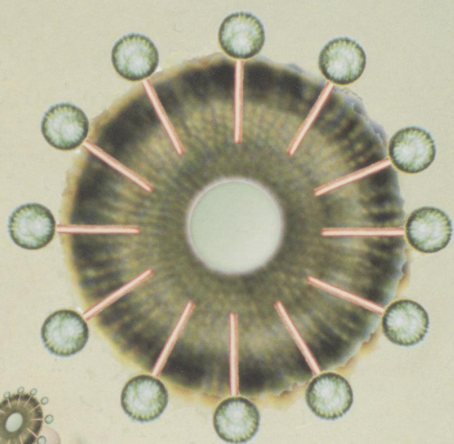


University of Kentucky Research
Fall 2003

Odyssey



Inner-Space Invaders

Nanoparticles Delivering
Knockout Drugs

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Two UK researchers are creating nanoparticles loaded with cancer-killing drugs. The tiny spheres are further engineered to target and infiltrate specific diseased cells.

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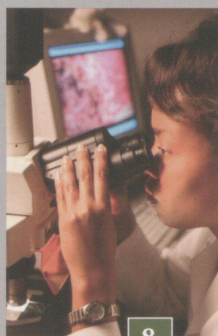
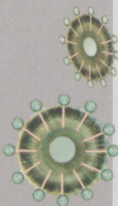
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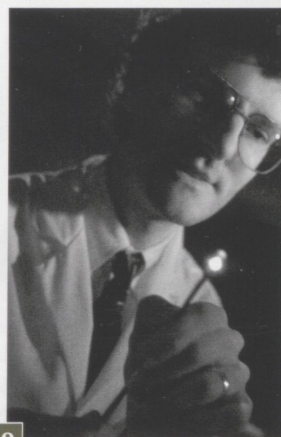
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A grayscale microscopic image showing two large, irregularly shaped cells with textured, bumpy surfaces. Numerous small, spherical nanoparticles are scattered around and on the cells. Some nanoparticles have a distinct central core and radiating lines, resembling viruses or engineered particles. The background is a light gray with some faint, out-of-focus structures.

Inner-Space Invaders

Nanoparticles Delivering Knockout Drugs

WRITTEN BY
Jeff Worley

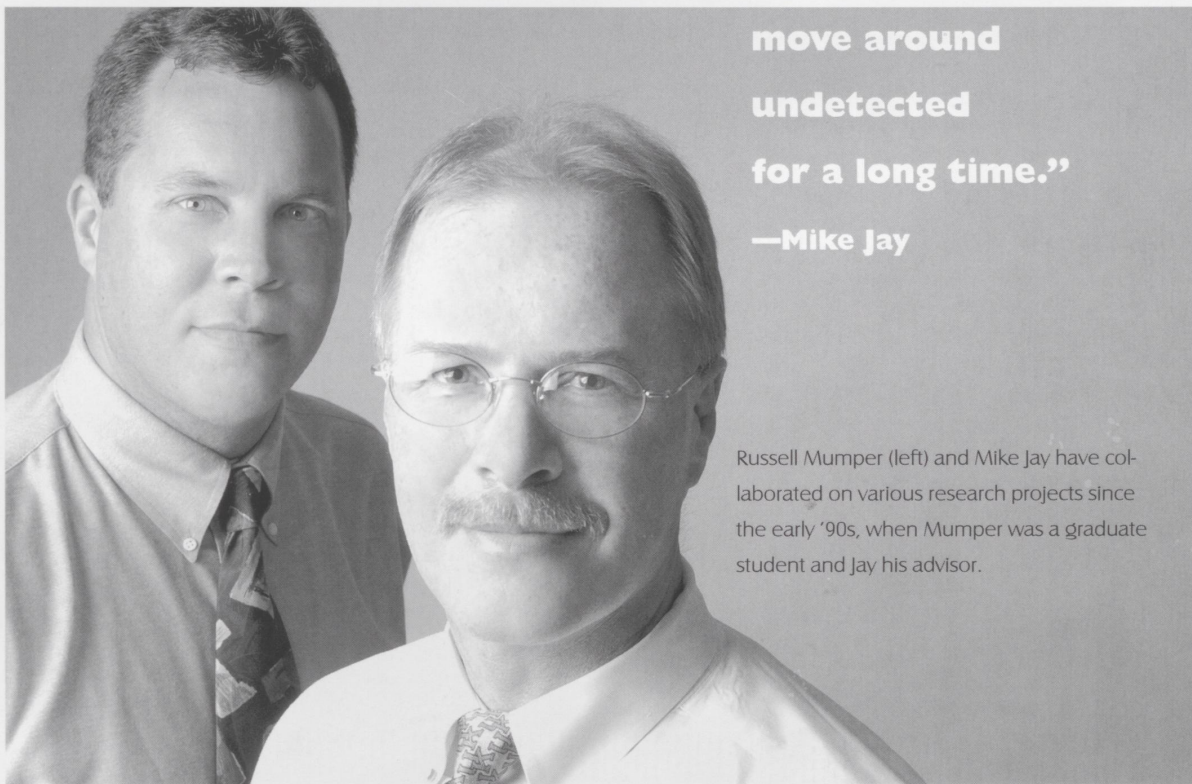
Armed with therapeutic drugs, nanoparticles injected into the body move along in the bloodstream toward their target—a cancer cell. The mighty macrophages spot a few of them and gobble them up. But these nearly invisible legions of stealthy, infinitesimal specks make it past almost all the sentries, invade the target cell, and release their potent drugs.

This scenario is being perfected by Russ Mumper and Mike Jay in the University of Kentucky College of Pharmacy. Mumper's recent work with nanoparticles, funded by the NIH National Institute of Allergy and Infectious Disease, holds great promise for treating various cancers and fighting viruses like HIV.

"Mike and I are involved in several projects to deliver drugs in new and better ways," says Mumper, an assistant professor of pharmaceutical science who returned to UK four years ago after spending seven years in industry. "Using

“Basically, the bigger the particle—the more noticeable a foreign body is—the more attention it attracts. So nanoparticles can move around undetected for a long time.”

—Mike Jay



Russell Mumper (left) and Mike Jay have collaborated on various research projects since the early '90s, when Mumper was a graduate student and Jay his advisor.

nanotechnology, we're able to package drugs in tiny spheres and send them to specific cells."

Nanoparticles continue to gain attention and earn respect. They're so small they are measured in nanometers—billionths of a meter. To put this in perspective, the width of this letter "I" is about a million nanometers.

"The essence of nanotechnology is the ability to work at the ultra-small level," says Jay, a professor of pharmaceutical science and director of UK's Center for Pharmaceutical Science and

Technology [see sidebar, p. 4]. "Simply put, the engineering idea is to design things from the inside out at the nano scale to create exactly what we want. Nanotechnology offers limitless possibilities in the fields of pharmacology and medicine. It provides new ways for us to deliver specifically targeted, potentially life-saving drugs."

Tinkering with the Very Tiny

In the battle against cancer and other devastating diseases, pharmaceutical

companies are developing new drugs every day. Many of these drugs work fine in cell culture tests but then fail the crucial water test.

Around 40 percent of all newly discovered compounds have poor water solubility or none at all. This is a problem because the human body is a huge reservoir of water—we're two-thirds water. "Lots of drugs get killed along the developmental pipeline because they can't be formulated to be used in the body," Jay says.

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UK's Center for Pharmaceutical Science and Technology

On its hopeful way to FDA approval, a drug is poked and prodded, weighed and measured. Every move it makes is analyzed and then reanalyzed. The process is tricky, time-consuming and daunting. But at UK's Center for Pharmaceutical Science and Technology (CPST), this process is streamlined in the manner of one-stop shopping.

"We're a full-service facility," says Mike Jay, director of the center and a professor in UK's College of Pharmacy. "We can work with someone from the idea stage all the way through Phase I and early Phase II manufacturing of the drug for clinical trials, and we can do all of this right here in the College of Pharmacy building." Phase I testing involves giving a drug to a small number of people to see what dose is safe; Phase II testing entails giving a larger number of participants the appropriate dose over a longer period of time to see if the drug is working and whether it has any long-term side effects.

The CPST, which opened its doors in 1986, has formulated drugs into injectable liquids, freeze-dried products, tablets and capsules, dermatological products, and produced up to 5,000 units at a time. UK is one of two university-based, FDA-registered pharmaceutical manufacturing centers with the unique ability to freeze-dry products. To date, the CPST, which utilizes strict, current Good Manufacturing Practices, has completed over 200 contract projects.

"We target four classes of clients: university researchers, biotech companies, pharmaceutical companies that gross \$25 million to \$250 million a year, and the NIH," says Frank Manella, managing director of the center. He adds that the center has increased client billings from \$200,000 in 1996 to \$1.5 million last year. "We've been on a pretty solid growth curve, thanks to the leadership of Dr. Jay and the College of

Pharmacy's solid support. We plan to take it even higher—to \$10 million plus by 2007."

Manella, who was hired in November of last year, is a "wonderful, new addition" to the center, Jay says.

Manella started out 30 years ago as a bench research chemist, working on new semi-synthetic penicillins. He eventually ended up heading Pfizer's worldwide sterile penicillin packaging and freeze-drying operation in Terre Haute, Indiana.

"I got involved in new business development along the way and traveled extensively in the U.S., Japan and Europe looking for new pharmaceutical compounds to license, develop, and finally—after FDA approval—market to physicians and pharmacists," Manella says. "This is much the same thing the CPST does for its current clients." He says he wanted to come to UK because of the ambience of a university setting—the camaraderie, curiosity and stimulation he saw here when he worked last year with the College of Pharmacy as a consultant.

The CPST will be growing soon, and moving. "We'll be moving to UK's Coldstream Research Campus [near the crossroads of I-75 and I-64, six miles from the Lexington campus] next year and plan to open our doors early in 2005," Manella says. "We're hoping that our presence there will also entice the building of commercial manufacturing facilities alongside us. That way entrepreneurs could easily segue from Phase II to Phase III clinical manufacturing and then scale up for commercial quantities."

"We'll retain the current facility here in the College of Pharmacy building, too," Jay says. "What will happen is the manufacturing of sterile products will be done at Coldstream, and the manufacturing of non-sterile products will continue here on campus."

Manella mentions another tangible benefit of the CPST expansion.

"Historically, way too many of the top College of Pharmacy graduates leave Kentucky. I'd love to see some of this brain drain stop."

The center will provide the opportunity for UK graduates and others to put their skills to work right here at home. "We hope to add more than 40 people to the center in the next 12 to 18 months," he says, "and if things go according to plan we could be up to around 100 people at Coldstream doing a three-shift operation by 2007."

Frank Manella is managing director of UK's Center for Pharmaceutical Science and Technology (CPST), one of two university-based, FDA-registered pharmaceutical manufacturing centers with the unique ability to freeze-dry products.



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So here's the research challenge: How do you increase the water solubility of a drug that doesn't want to dissolve in water?

"In order for a drug to be injectable or to be absorbed from the stomach, it has to show some water solubility," says Jay. "One way to do this is to fake it—put the drug into an environment in which it is soluble, an oil droplet, for instance, and send it into the body this way." This idea is at the heart of the

researchers' new patented process, which they term "nanotemplate engineering."

"The drugs that we would like to formulate are not very water soluble, but they are soluble in oil," Mumper says. These minuscule spheres—under an electron microscope they look like a cluster of marbles—can be engineered to seek out a particular tissue or cell in the body. After the drug reaches its target, a cancer cell, let's say, the drug

is welcomed in and is released from the particles. It then leaches out into the cell, killing it.

But everybody knows water and oil don't mix. So how do these designer particles manage to pass through water to find their designated target? The answer, Jay says, has to do not only with size but also with chemicals called surfactants.

"To make oil and water mix, we resort to a bit of scientific trickery," Jay

“Kentucky-based businesses like NanoMed can help keep some of our top graduates from leaving Kentucky.”

—Russ Mumper

says with a hint of a smile. “A surfactant is a surface-active agent—hand soap is a good example. In our case, it’s something that will align at the interface between oil and water.”

The surfactant they add to their mix, he explains, has an oil-friendly part that extends into the droplet and a water-friendly part that lies on the surface of the droplet, virtually surrounding it. The surfactant serves as a kind of mediator. It’s what permits, in large part, the unlikely marriage of water and oil. The purpose of the surfactant is to stabilize the oil droplet, to keep it well suspended.

“These microemulsions are stable,” Mumper says. “They won’t separate over time, like oil and vinegar will, for example, and this stability is exactly what we want.” He adds that he and Jay have carefully chosen an oil that is a liquid at slightly elevated temperatures (120° F or so), but at room temperature is a solid. “When we cool the mixture back to room temperature, the droplets transform into tiny, solid particles. [Substances that can change form are fairly common—think of water and ice.] They have the drug inside them, and they’re still coated with the surfactant.”

The researchers’ nanoparticle tinkering doesn’t stop here. “By using ‘recognition molecules’ attached to the surface of the particles, we can direct them to specific parts of the body, say, a receptor on a tumor,” Jay explains. Nanoparticles can be easily injected or can be dried and incorporated into a tablet, he explains. “The particles head for the cancer cell and bind to a receptor. What we hope will happen then is that the cancer cell will engulf the particle and, in doing so, engulf the drug that will leach out into the cell.”

A Magic Bullet

“People might wonder, ‘Why nanotechnology? Why nanoparticles?’” Mumper says. “Well, there’s one primary reason. To be effective, more and more drug therapeutics have to be delivered to specific cells, tumor cells in the brain or in the liver, for example. And of course these cells have to be able to recognize and take up the material.”

Nanoparticles are so small, Mumper says, that cells can easily take them in—the typical cell is around 8,000 nanometers. “It’s kind of like a magic bullet. It’s a way to target specific nefarious cells without damaging healthy cells in the same neighborhood.”

And Mumper gives another reason why these miniscule warriors are so effective—they can circulate in the body for a relatively long time without being removed by macrophages and other cellular police.

“Basically, the bigger the particle—the more noticeable a foreign body is—the more attention it attracts,” he says. “So nanoparticles can move around undetected for a long time.”

Another important thing about their process, says Jay, is that it’s inexpensive. Instead of using pricey fluidizers, homogenizers and other equipment that can be used to make new pharmaceutical products, the researchers simply let nature take its course.

“We literally throw the materials in—a mix of oil, water, surfactant, and the drug—and gently mix them together,” Jay says, adding that the materials they use to make nanoparticles are all FDA-approved for use in humans. He and Mumper have patented this method of making nanoparticles, one of six patents they hold jointly in the field of drug delivery.

A Special Collaboration

“As a junior chemistry major at UK in ’86, I needed to do independent research as part of my coursework,” Mumper recalls. “I could have done it in the chemistry department, like most chem majors do, but a friend of mine in the College of Pharmacy convinced me to go work there. I did, and Mike became my mentor.” Mumper adds, with a smile, that Jay was good enough to allow him to make mistakes “all on my own, which accelerated my learning curve.”

Jay was Mumper’s graduate student advisor from 1988 to 1991, and around that time they co-authored six papers. “Russ was a very capable student and a solid researcher from the beginning,” Jay says. “One of the first things you learn as a faculty member working with graduate students is that the goal is to make them better than you. I’ve definitely met that goal with Russ.”

Over the years they stayed in touch, keeping each other up to date on their research, while Mumper was working in industry with Burroughs Wellcome and, later, GeneMedicine in Texas. Then in 1999 Mumper returned to UK as one of the first new faculty members hired through the Research Challenge Trust Fund (RCTF) initiative, commonly known as Bucks for Brains.

“In ’99 the company I was working for was sold, so this was a good time to look around,” Mumper explains. With “substantial help” from Bob Blouin, former associate dean of research and graduate studies in pharmaceutical sciences, Mumper was offered the job of assistant director of the Center for Pharmaceutical Sciences and also a tenure-track position in the College of Pharmacy as RCTF faculty.

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"This was an ideal position for me," Mumper says. "I knew I'd be able to do research on drug-delivery systems and teach, but also, as assistant director of the center, do a lot of product development, which is exactly what I'd been doing in industry."

When Mumper came back to UK, Jay's lab was working on water and fluorocarbon microemulsions for drug delivery to the lung, and Mumper had recently been working, in industry, on ways to make small particles.

"So Mike and I started talking about this, and I said, 'Have you ever tried making a particle in those microemulsions?' Mike said no. 'What if we took your fluorocarbon microemulsion and tried to make particles within the individual droplets?' We did some experiments and it worked." Mumper says this integration of their research backgrounds and experience is typical of how they collaborate.

The Business of Research

Among their discussions after Mumper's return to UK was the idea that they should think about forming a company together sometime down the line, an enterprise that would get them into the drug-delivery business.

"We started submitting invention disclosures related to our work with microemulsions and nanoparticles, and thought we might form a company in four or five years to license these intellectual properties," Mumper says. "But then after about a year and a half we decided, why wait."

"Our work was coming along well, and we'd been watching new developments, reading the literature closely. So we decided that if we waited, we could

getscooped," Jay says. The result of this forging ahead was the birth in 2000 of NanoMed Pharmaceuticals Inc. Co-founders Jay and Mumper were joined in 2001 by Stephen Benoit as the company's CEO.

"Russ and I went to a venture fair in Kalamazoo, Michigan, and made our presentation about the nanoparticle work we were doing," Jay explains. "Afterwards, Stephen came up to us and said he liked what he'd heard. He told us about his background, which is very impressive, and then he said, 'How would you guys like a CEO?' It was a very serendipitous meeting." Benoit, who holds an MBA in finance, brings to this venture over 20 years' experience in biotechnology, disease-management, pharmaceuticals, and finance services industries.

Jay explains that NanoMed is focusing on translating their research into the marketplace, and despite the economic downturn in the United States in the last couple of years, market oppor-

tunity is good, he says. "The global market for advanced drug-delivery systems was more than \$16 billion in 2000 and is estimated to grow to more than \$27 billion in the next five years."

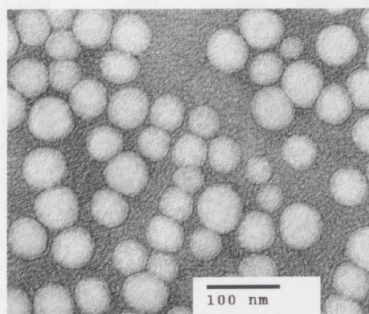
"Resources are NanoMed's biggest challenge, no doubt," says Mumper. "Our labs continue to do well, and we'd like to commercialize this technology for biomedical applications, but you need money to perform the safety-toxicity studies in animals and do early clinical trials."

The general rule for product development, Jay adds, is that each product costs about a million dollars to get into clinical trials. "Then the weeding process starts," he says. "Of every 250 drugs that enter clinical trials, only one will get approved by the FDA. So drug companies and investors sink a lot of money into the process in hopes of the big score. People should understand that this is why drugs are so expensive. It's not because the companies are overpaying the scientists," he laughs.

But Mumper is undaunted by these challenging stats.

"A primary reason I came to UK," Mumper says, "is because I was ready to make a long-term investment in this research and translate it to market. It's also an investment in our state. Kentucky-based businesses like NanoMed can help keep some of our top graduates from leaving Kentucky."

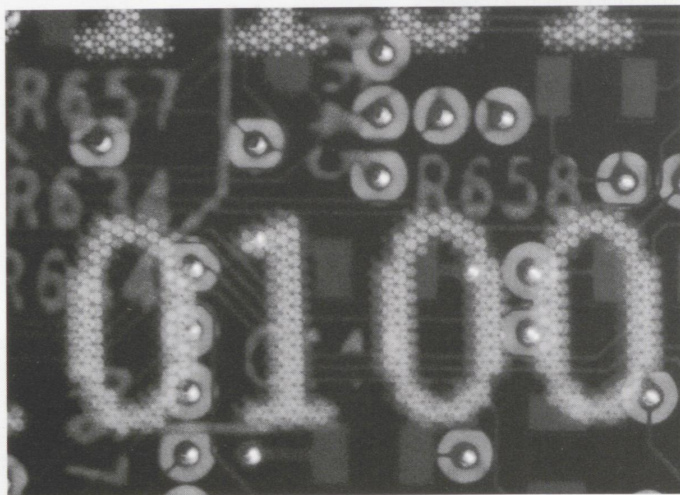
"My greatest hope," says Jay, "is that some of our technology will make it to commercial products. In 15 years I'd like to be able to look back and say, 'Not only was it a great ride, but what we discovered and developed is being used to help people in measurable ways.'"



The nanoparticles that Jay and Mumper design—under an electron microscope they look like a cluster of marbles—are engineered to contain a cancer-killing drug and to seek out a particular cell in the body. After the particle reaches its target and is welcomed in, the drug is released into the cell, killing it.

WRITTEN BY
Alicia P. Gregory

Shaping the Future of Software



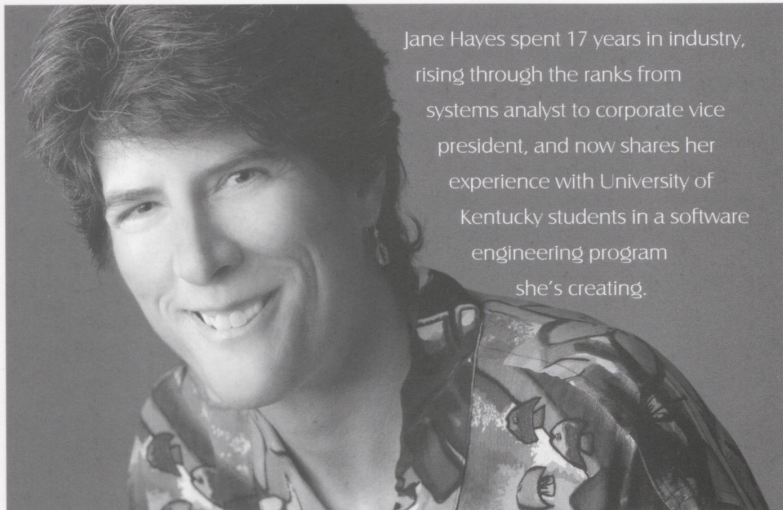
"I'm worried about your daughter," the kindergarten teacher told Jane's mother over the phone. "She's drawing hieroglyphics everywhere."

The parent-teacher conference the next day revealed the source of the mysterious symbols—Dad.

A captivated five year old, Jane would sit at the dining room table each night with her father's computer printouts, copying the Greek symbols—deltas and sigmas. "To this day my handwriting is all crazy—I don't form any of my letters correctly—because I taught myself to write from his printouts.

"My mom loves to tell this story," Jane Hayes adds, laughing.

This encounter may have ruined her penmanship, but she didn't abandon computers. In fact, Hayes went on to spend 17 years in industry, rising through the ranks from systems analyst to corporate



Jane Hayes spent 17 years in industry, rising through the ranks from systems analyst to corporate vice president, and now shares her experience with University of Kentucky students in a software engineering program she's creating.

vice president, and now shares her experience with University of Kentucky students in a software engineering program she's creating. Her goal: design software to further UK research and empower students to tackle real-world problems. As an assistant professor of computer science, Hayes is addressing these problems through ongoing research on software maintainability and reliability. And programs used by NASA and other industrial partners, as well as software written by her own students, are the subjects of her experiments.

Girl Power

In response to the perennial gender question about women in her field, Hayes shares an experience from a recent international conference on software engineering: "Of three keynote addresses, one was given by a very impressive woman, and it was titled something like 'Women in Computer Science: Must There Be So Few?'"

In the hour-and-a-half talk about her NSF-funded research, the speaker

recounted her focus-group findings and gave international stats, such as how more women than men work in computer science in Singapore. "Then she showed the U.S. stats in industry and academia, and, of course, it's very depressing," Hayes says.

"But as someone who has been the only female in most of my organizations, I'd say this to the conference organizers: it would have been more effective if you had a male give the speech on 'why so few women?' and if you had a female give a technical keynote.

"I think it leaves the wrong impression with the young males in the audience," Hayes says and pauses, "who are really the ones that you need to worry about. Most of the professors around here get it; they value equality and diversity. But what the young up-and-comers will remember from this conference is, 'Oh yeah, there was only one *girl* who gave a keynote, and all she did was show a bunch of stats about why there aren't more *girls* in computer science.'"

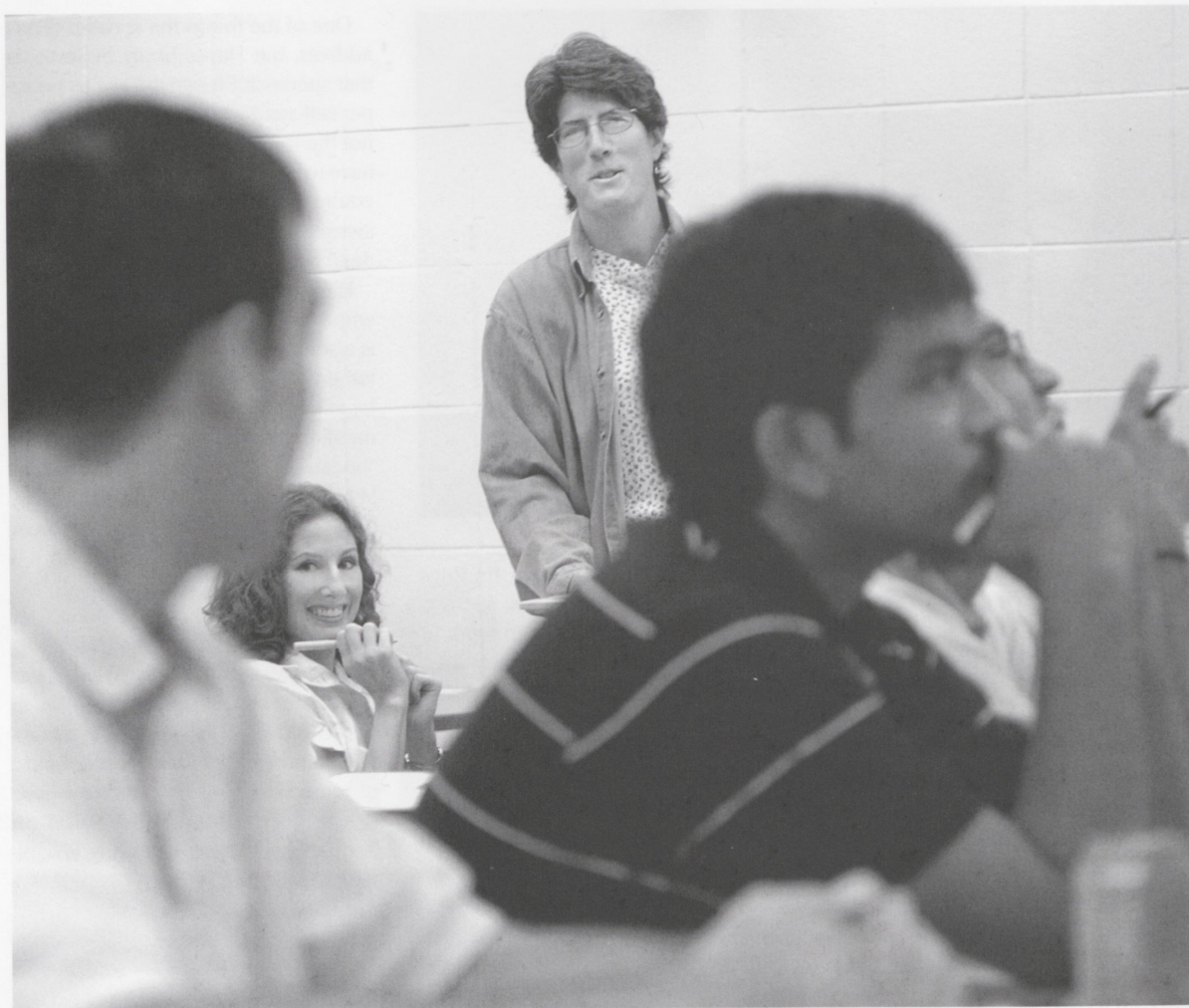
One of the things the speaker didn't address, but Hayes firmly believes, is that successful females have to be super self-assured. "You have to say, 'I'm not the token female. Bring it on.' You have to be just cocky enough to believe you're getting this job because you're awesome, not because of your gender."

Hayes says she owes some of this empowered attitude to her mother, who is also in the computing field, and her father. "I'd be curious to see how many female engineers were daughters whose daddies didn't have any boys," she says, "because that's the case in my family. My dad had two girls. And that may have something to do with my career choice—if Dad believes I can do it, I can."

Long before the advent of "Bring Your Daughter to Work Day," she'd tag along with her parents to work. "While I was there I taught myself to program in BASIC and FORTRAN on ancient computers most people have never heard of," says Hayes, an Ohio native whose family moved around a lot based on her dad's positions, including Wright-Patterson Air Force Base, General Motors ("He was one of the inventors of the V-6 engine," Jane says with obvious pride), Imperial College in London, England, the Air Force Academy, and the University of Southern Mississippi, where he was vice president for academic affairs.

Hayes attended Hanover College. The liberal arts school on the Indiana-Kentucky border didn't have much in the way of computers, she says. Hayes started out in what she calls a "fluffy" major—political science—but decided in her junior year to add geology as a double major. The geology department had something

Shaping the Future of Software



(From left) Trevor Barnett, Sarah Howard, Jane Hayes, Karthik Ramkumar, and Ramkumar Singh talk about life-cycle models for software development in CS616, one of three graduate-level software engineering courses Hayes has created since coming to UK in 2001.

special to offer—one computer.

When she got out of college, Hayes took computer science classes in the summer. Then, based on her geology degree and experience with maps, as well as limited computer programming experience, she got hired by the Defense Intelligence Agency. "They wanted government employees to be able to do all of the computer programming. They told me to learn this guy's job so they didn't have to contract it out," she says. The task involved cracking the code of a programmer/baseball fanatic.

"He thought he'd be really cute and name all his variables after baseball players. So I had to try to figure out how this program worked with Joe DiMaggio and Pete Rose—totally meaningless variable names. It was a digital imaging system, so it was very complicated." This experience instilled a career-inspiring passion in Hayes—software maintainability—"writing software that other people can easily modify." After deciphering the inner workings of this Top Secret system, used to maintain a database of aerial photographs, Hayes was hired as a senior systems analyst at Science Applications International Corporation (SAIC) in 1984.

"SAIC is the largest employee-owned technology company in the United States," Hayes says. "It was formed by a small group of very entrepreneurial nuclear physicists, who were committed to sharing the wealth. They set up an internal stock market—you can only have stock if you're an employee—and it's generated many, many millionaires."

Hayes's projects at SAIC, including the Navy's Tomahawk cruise missile system and nuclear power plant control systems, involved writing software with life or death ramifications and the

concept of verification and validation.

"Validation is making sure that you built the right software. Verification is making sure that you built the software right," Hayes says. "Anytime you need to trust a software system with anything that could involve potential loss of human life, damage to the environment, or loss of huge sums of money, you should be willing to spend the extra money on software verification and validation to make sure that you've done everything possible to minimize that potential risk."

Hayes spent 16 years at SAIC, and by 1999 as corporate vice president she was managing more than 230 employees, one \$50 million contract, and a \$35 million-a-year business unit.

"At SAIC I felt that they treated me like an engineer or like a manager, that my gender didn't matter," Hayes says, laughing. "I certainly didn't see them holding me back." When she started at SAIC, she was one of two female engineers; when she left SAIC, the company was about 25 percent female.

"I bet I got calls every month asking me to start my own company. Groups of people within SAIC would say, 'Start your own woman-owned business. We'll all come and work for you.' But I didn't want my own business. I knew how hard it was being a manager at somebody else's company, and I was already working too much."

Hayes continued to work at SAIC and in 1990 started her Ph.D. while she was pregnant with her daughter, Chelsea. "Every time I would get a promotion, SAIC would give me 10 new people to oversee. My advisor at George Mason University, Jeff Offutt, would ask, 'How many more people? Ten more obstacles to finishing that Ph.D.' He'd tease, 'You're never going to make it.'"

But Hayes was determined. She finished her Ph.D. in 1999, five years after having her second child, David. She says getting her degree is a testament to her husband Greg's strong support and was inspired by her mother's return to—and completion of—college at age 47.

Act II: Academia

"I was to the point where I had to commit to executive management for the rest of my career," Hayes says, "but I'd been itching to go into the academic world for quite a while. I figured this was really my last chance to go and do something different."

That itch led to an interview at UK. Mirosław Truszczynski, computer science chairman, says, "She definitely had strong academic credentials, our primary consideration, but what truly set Jane Hayes apart from other people in the pool was her significant industrial experience. That is very important because we need people who can relate their own experiences to our students and who can convincingly speak about what careers await them."

"She had a very clear vision, which I thought was quite different from the rest of the people we interviewed. She knew what she wanted to do." Hayes would be tackling more than the usual responsibilities of developing a research program and teaching students; her teaching role would involve building a curriculum from scratch because there were no software engineering courses at UK. "She was looking for that type of opportunity," Truszczynski says.

Hereagerness was important because the department knew the absence of software engineering was a weakness of the UK program, he says. "Over the years, in conversations with people in

The computer science department has 200 graduate students and between 400 and 500 undergrads.

computer and software companies in the Lexington area, they had complained about a lack of understanding—not only in our graduates, but in graduates from other programs as well—of the process through which software is designed, assessed and redesigned.”

Since her arrival at UK (under the Research Challenge Trust Fund initiative) in January of 2001, Hayes has developed three graduate-level courses. “Her classes have very high enrollment. There would probably be 40 to 50 students in each class if we let them—we try to limit it to 30 to 35 students—but there’s certainly more interest than seats in the class,” says Truszczynski. The computer science department has 200 graduate students and between 400 and 500 undergrads.

UK is a different world from industry, but not one for which Hayes was unprepared. “I had a lot of friends at SAIC who were very worried about me switching worlds. ‘It’s going to be too slow paced for you.’ ‘You’re going to hate all the bureaucracy.’ And they’ve been wrong,” Hayes says.

“Dr. Truszczynski is a top-notch chairman, and I’ve been really impressed with Dr. Jim Griffioen, who runs the Laboratory for Advanced Networking [and is Hayes’s neighbor in the Hardyman building]. And I’m blessed with a wonderful mentor, Judy Goldsmith.” Goldsmith is an associate professor in the computer science department.

“My friends at SAIC tease me because I’ll say, ‘We just got a \$46,000 grant! We’re doing great.’ And they’re like ‘What? If we came to you and said we just got a \$46,000 subcontract—you’d say, For a month?’” While the dollar differences are substantial, Hayes says, the interaction with students is a reward in itself.

Data Fixes for Drug Discovery

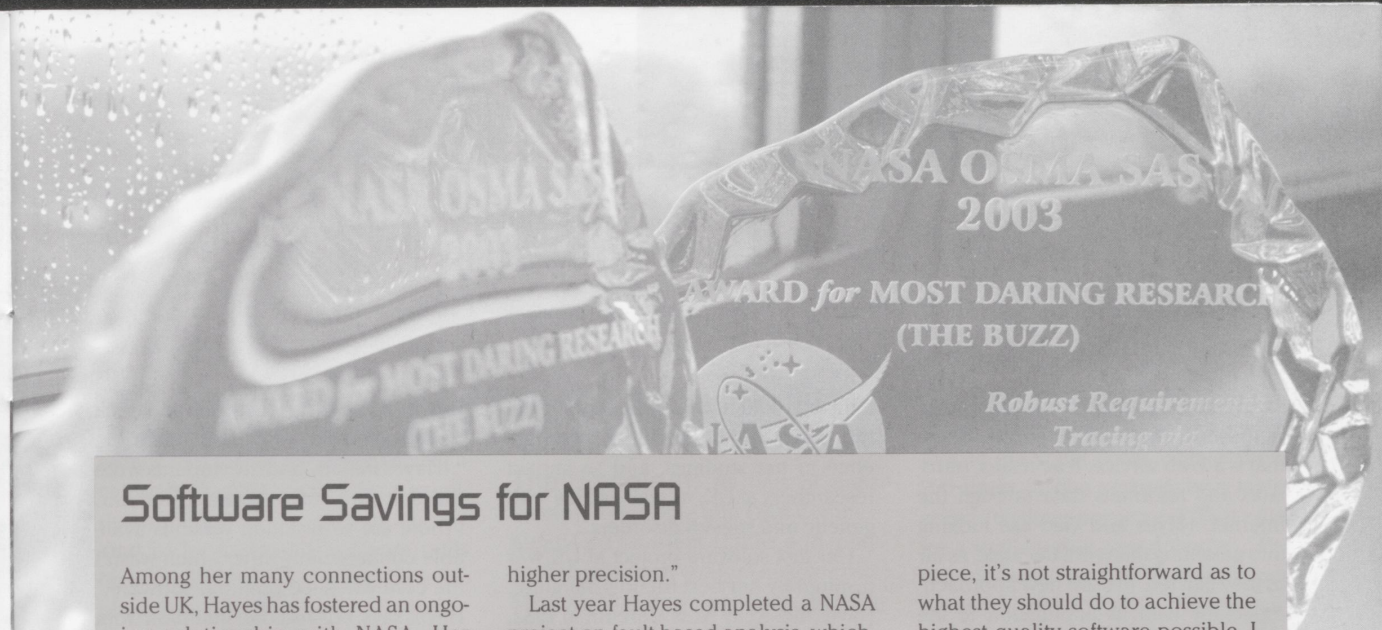
One of Hayes’s top students, Tina Gao, came up with an idea to put drug discovery on the fast track. Gao, who did undergraduate work in her native China, followed her husband from Penn State to Lexington when he decided to join UK’s computer science program. Her background is in one of the hottest areas in life sciences—bioinformatics (acquiring, archiving and analyzing biological data).

Gao cites the human genome project as the best-known example of bioinformatics. “There are 30,000 genes in the human genome. My goal is to use computer science to solve a lot of data analysis problems in bioinformatics,” she says.

She states the problem: research labs and universities around the world have developed computer systems, in various programming languages, to do parts of the 15-step process you run gene sequences through on your way to discovering new drugs. The challenge comes in when you get data out of one system, and the system for the next step can’t “read” it because it doesn’t expect the data in that particular format. It’s a compatibility problem.

“Biology people are not computer professionals, so it is very difficult for them to understand the logic of each system and how to integrate those systems together,” says Gao. “So what they actually do is get a result from one system and manually transport it [reformat it by hand] into another system. But with the big success of the human genome project and the tons of data that are generated, it will be very difficult for people to do what they did manually before. We really need some automatic way to integrate all those systems together.”

continued on p. 14



Software Savings for NASA

Among her many connections outside UK, Hayes has fostered an ongoing relationship with NASA. Her current project is a collaboration with Alex Dekhtyar, a UK assistant professor in computer science and a Russian national, whose background proved to be an initial stumbling block.

"After the shuttle crash, NASA wasn't sure about letting non-citizens look at their data," Hayes says. "It took us a long time to get an agreement in place, but they decided to let Alex work on this. However, they're not allowing any of our non-citizen students to look at the data."

This project focused on improving "requirements tracing," which means making sure every line of code is fulfilling one of the goals set for the software from the beginning. And the project netted the "Most Daring Research" award from NASA on July 30 of this year. The award is dubbed "The Buzz," in honor of astronaut Buzz Aldrin, who pioneered the idea of manned orbital rendezvous. Hayes says, "They felt we were daring to compare our approach to the de facto standard, a tool called SuperTrace. Our work has advanced and now we are out-performing the standard."

"We measure two things: recall and precision. Recall looks at whether or not we are finding all the items we should, and precision looks at how many incorrect items we are finding. Our recall is much higher right now than that of SuperTrace, with slightly

higher precision."

Last year Hayes completed a NASA project on fault-based analysis, which, in a nutshell, identifies cause and effect. "In software engineering we get an indication that something went wrong, and we call that a 'failure.' We call the cause—which isn't always easy to identify—the 'fault.'"

NASA gave Hayes 17,000 fault reports, going back 15 years. "They basically gave us everything in their fault database."

When you talk about the International Space Station, Hayes says, you have millions of lines of code and billions of dollars in hardware and software, with 13 countries working together. "Obviously this is a huge management challenge, but just looking at the software

piece, it's not straightforward as to what they should do to achieve the highest quality software possible. I could list 57 different approaches off the top of my head."

Hayes's research shows NASA how to get the most bang for their buck. "The whole idea here was to build a taxonomy of faults. The first thing I did was ask, 'What are the types of faults you see occurring across all NASA systems?' My taxonomy had 18 categories, but I found 85 percent of the faults fell into three of those categories. That information in and of itself was of huge value to NASA—now they know where to focus their efforts."

This isn't sexy stuff, Hayes says, but it's important.



Jane Hayes and Alex Dekhtyar won the "Most Daring Research" award from NASA in July 2003.

And that's what she's built for three of these 15 steps—a generic interface that is a Web service. It accesses, translates and reformats data through the Internet. Hayes and Gao are looking into patenting this work because, as far as they can tell, this is a new approach, especially with its application to life sciences research.

Gao, who is wrapping up her master's studies, says both she and her husband agree that Hayes is one of the best advisors they've ever had. "She gave us a lot of advice on academics, and she was very considerate of our different cultural background. We appreciate that," Gao says.

Kid-friendly Software

In starting her own research program, Hayes looked for software applications that would allow her to gather the kind of stats that are her bread and butter. In software maintainability monitoring—trying to estimate how long and how much money would be required to take over somebody else's code (something technology companies need to know, but have no clear method for estimating)—she needs to take measurements of many different software programs at different stages of development.

"It's just like when you go to the doctor," Hayes says. "They measure blood pressure, temperature, height, and weight. We have data that we collect on programs—things like number of lines of code. We're trying to figure out if any of those things correlate with the actual time it takes for somebody to change a program, because if we can find those correlations, we can build models to help with cost estimating."

But Hayes has taken a unique approach to gathering her experimental

data: she sees her work as an opportunity to give real-life engineering experience to her students, and to impact researchers at UK, as well as kids with genetic and speech disorders.

Her first software project at UK was inspired by her best friend's daughter. Hayes met Kelly Noss Marcum in 1982, when they were sorority sisters at Hanover College. Hannah, Marcum's daughter, was diagnosed with phenylketonuria (PKU).

The Problem: PKU is a rare, inherited metabolic disease that, without treatment, results in mental retardation and other neurological disorders. "People with PKU can't metabolize phenylalanine [an essential amino acid]. So phenylalanine, which is a subset of protein, builds up in their body and kills brain tissue," Hayes says. The level of enzyme deficiency varies among children with PKU, but most must adhere to a strict diet that eliminates all high-protein foods. That means no meat, fish, poultry, milk, eggs, cheese, ice cream, nuts, and many foods that contain regular flour.

Newborn screening, by way of a heel prick to test blood for high levels of phenylalanine, has been mandated in the United States since the mid-'60s. One out of every 10,000 babies born in this country has PKU; several hundred infants are diagnosed and put on a restricted diet each year.

The Goal: Help kids with PKU and their families keep track of their phenylalanine milligrams.

The Assignment: Write a piece of software that incorporates the USDA nutritional database that will help

people with PKU choose food and track daily and weekly milligram intake.

Hayes initially had the students write the software for a home computer. "There are workstation versions available commercially now, which wasn't the case when we built our software," Hayes says, but adds her intention from the beginning was to start with the workstation version, then throw what she calls a "major modification" at the students—requiring them to adapt their code to run on a PDA.

PDAs, or personal digital assistants, are mobile, hand-held devices (essentially mini-computers) that many people use to keep calendars and addresses. Common PDAs include 3Com's PalmPilot and Compaq's iPAQ, and typically range in price from \$100 to \$700, depending on processor speed and graphics quality.

The Challenge: PDAs are convenient from a user's standpoint, but troublesome to a software engineer. "The PDA takes us back to the dark ages of having to worry again about memory and processor speed," Hayes says, adding that the most popular PDA, a PalmPilot, is hard to write software for because of the small amount of memory. Her students have had the most success programming for the iPAQ. "Palms have around 8 MB; iPAQs have 64 MB."

The Result: "The beauty of having a program that tracks phenylalanine milligrams on a PDA is you don't have to write down what you eat," Hayes says. Right now, most people with PKU or their parents have to keep track of food by hand then type it into Microsoft Word or Excel.

"Plus, it really helps in the decision process." Hayes shows the graphic interface that allows the user to select a category like "Vegetables" from a pull-down menu. "They can look up any kind of food, and the software pulls from the USDA nutrition database the phenylalanine milligrams and calories. Even some fruits and vegetables, like corn on the cob, are high in phenylalanine, so kids with PKU really have to watch what they eat." The software keeps a running tally of milligrams for the day and week.

Hayes hopes to develop the software to the point where the kids can take the PDA home, put it in the cradle—the base that sends information stored in the PDA to their personal computer—and generate reports that they could e-mail to the doctor before their next checkup.

UK has taken the first step toward patenting this technology, and Hannah Marcum, who is 15, is carrying the software, called the PheTracker, on her PDA. She submits "bug reports" when she has a problem with the software. "We have a volunteer student group at UK helping to correct these bugs," Hayes says.

"We have 10 families lined up to borrow the iPAQs with this software once we release it. We were specifically targeting preteens, because they're just getting old enough to do this on their own." Hayes adds, "Schools won't let kids carry PDAs or cell phones, but the PKU kids could carry these with doctor's permission, so that makes them cool after all these years of being weird because they can't eat meat or dairy."

Practice Makes Perfect Speech

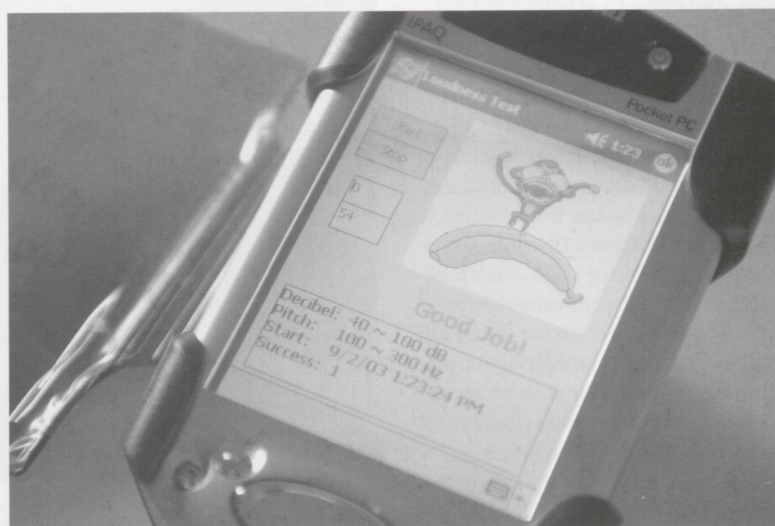
The Problem: As part of their therapy, kids come into UK's Communication Disorders Clinic and play speech games on equipment that costs \$10,000. "But they can't take that big computer, and all its attached hardware, home with them," says Jody Deem, associate professor and director of the division of communication disorders at UK. "Just sitting with a book and Mom or Dad at home is boring."

The Goal: Make it cool to do daily speech therapy practice at home. Target ages five to 10.

The Assignment: Create software (first for a workstation, then for a PDA or for the Internet) that uses the same kind of positive feedback the kids get with games on the big computer at UK.

The Challenge: "Speech is an enormous signal," Deem says. "In an adult female the vocal cords vibrate about 200 times in one second. In a male, about 100 times per second. That's just for a single vowel sound like 'ah.' For sounds like 's' and 'th,' the vibrations are at the level of 5,000 to 7,000 times in one second. So when you're talking about analyzing a child's speech for sound errors in a whole sentence, the computer needs to analyze thousands of data points each second." That's why the UK computers are so pricey. Is it possible to scale this down to work on a PDA?

The Result: Hayes's students focused on recording vowel sounds. They created software that incorporated positive feedback, say, when a child said "ah" loud enough, an animated bird flapped its wings or a monkey jumps.



Graduate students JenChi Cheng, Li Luo and Yan Zhang designed a jumping monkey for their PDA-based software program aimed at getting kids excited about their speech therapy homework.

"The students were so creative, and they had a lot of fun working on this project," says Hayes.

Deem was most excited about the Web-based software. "The average home computer has a lot more storage capacity and processor power than a PDA, so you can make even more cool reinforcements—more monkeys, more sounds," says Deem. "Some of the students even built in the ability for the speech language pathologist to log in and see how much homework practice the children have done and how many attempts they've gotten right.

"What Jane's students did is a wonderful step in the right direction in terms of taking speech analysis to a more portable level," Deem says. "It's not going to replace the big computer—the child will need to come in for the full-blown analysis at some point—but what the students did will keep a child fascinated by the speech therapy homework, and that's an accomplishment."

New Bones About It

The Problem: "I look at bone growth factors and their effectiveness for bone regeneration in the lower jaw," says Oneida Arosarena, an assistant professor of surgery who has been in the UK College of Medicine's Division of Otolaryngology for three years. She's looking at a lot of different variables: three types of bone growth factor (these are naturally occurring growth factors that normally shut off after your bones are done growing) and various carriers for the growth factors, like collagen.

"The ultimate goal of my research is to be able to reconstruct defects in the cranial-facial skeleton without having to harvest bone from other places, like the fibula or the hip, which requires



In her research on facial bone regeneration Oneida Arosarena, a UK assistant professor of surgery, is using the color-recognition software Hayes's students created.

lengthy reconstructive surgeries," says Arosarena.

A lot of people are working on the same problem, she says, but Arosarena's approach is different in that she is varying the dosage of the various growth factors. She is currently seeking grant funding to look at prolonged delivery of the growth factors, which are rapidly metabolized by the body. "If you can deliver them over a long period of time, you get better bone growth because that more closely replicates the normal healing process.

"Our method of evaluating new bone growth is where Jane's assistance becomes valuable," Arosarena says. She uses stereology—a method of assessing volume by doing counts of new bone in small sections throughout the sample tissue. Arosarena would use transparencies to lay a grid on top of projected images from her microscope. She'd use a hand-held counter to count points where the grid lines intersected with areas of new bone, marrow and soft tissue. This takes a long time.

The Goal: Speed up the process by creating an effective but inexpensive computer program.

The Assignment: Create a software program for a workstation, using color recognition, to automatically distinguish between bone, marrow and soft tissue.

The Result: "What we did was some pretty simple image processing," Hayes says. Arosarena explains, "The stains we use to process the tissue stain bone one color, soft tissue another. So the students programmed the software to recognize bone is pink and soft tissue is

blue. When we place a section under the microscope, it sends that image to the computer and the program acquires that image. Based on color recognition it can tell me how many points fall in the pink area. But what's really nice about this software is that I can override it.

"Sometimes when you transition from one tissue type to another, the color difference is not clear. So if I think the computer isn't labeling the tissue correctly, I can override it," she says. The computer doesn't eliminate the need for a trained eye.

"There are similar image-recognition products on the market [which average \$5,000], but they don't give you the option to override the computer's counts," says Arosarena. "I got a great program, and the students wrote it in one semester [Fall 2002]. I just had a paper accepted by the *Archives of Otolaryngology*, and I included all of their names in my acknowledgments. They at least deserved that, they were so much help."

Arosarena adds, "I can do now in two weeks what would take a month or more in terms of manual point counting."

Support Your Local Software Engineer

None of the three previous projects was sponsored research. Hayes says, "They were sort of grassroots things, started because I had students who needed to build a software product in a semester. I wanted them to have real-world customers, and I thought we should try to fill a need." Hayes would like to interest NSF and NIH in this research, and she says an NIH proposal with Joan Griffith, a UK assistant professor of pediatrics,

based on the PKU work is under way.

Hayes has already successfully garnered donations from a number of software companies to make her work possible. Programs like IBM's Rational™, JCover™ and CCover™ help students in the new software engineering classes write, build and test their own software. "We've gotten a lot of free stuff," Hayes says. "According to Rational, they gave us \$1 million in free software, so industry has been very good to us."

Department chair Truszczynski says, "That didn't just happen. In my opinion very few people have as much talent as Jane Hayes has in talking to people and exciting them about her ideas." ■

Odyssey

onlineexclusive

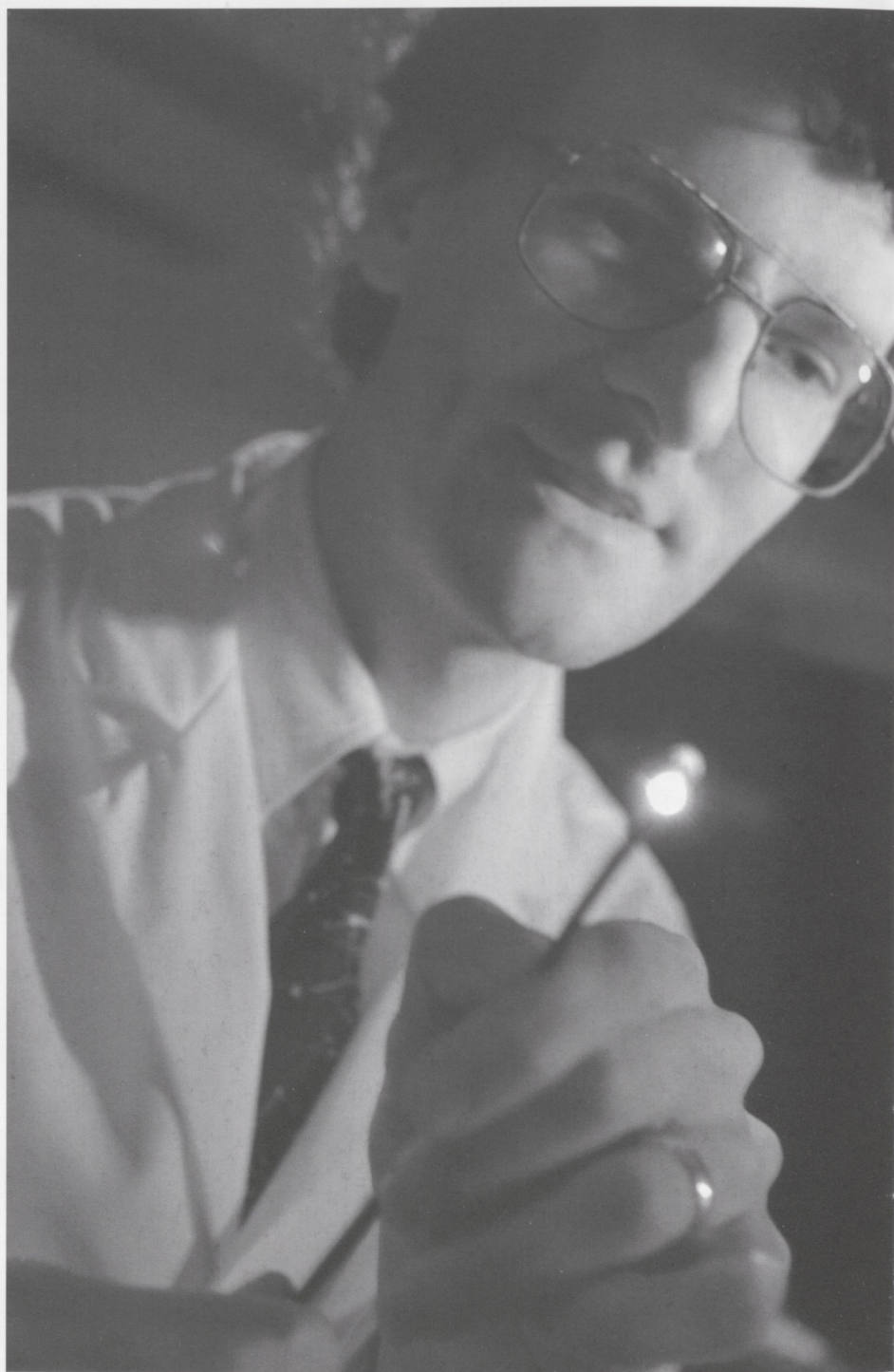
Since two issues of *Odyssey* a year can give you only a small sampling of the hundreds of important and exciting research projects at the university, we've come up with a way to further publicize work by UK faculty and staff: *Odyssey Online Exclusive*. It's our hope that these additional Web-based issues will provide a broader picture of research accomplishments at Kentucky's flagship university.

The inaugural issue, which you can find at www.rgs.uky.edu/ca/odyssey/exclusive, focuses on UK faculty who have started new businesses based on their research. One of these stories, on Rob Lodder's work with deadly arterial plaques and his invention of a fiber-optic catheter that can detect these deposits, follows here.

The online issue also features Boyd Haley (chemistry), Fred Payne (agricultural engineering), Linda Dwoskin and Peter Crooks (pharmacy), and Eric Grulke (chemical & materials engineering). A piece on Joe Fink, vice president for research and economic development, introduces the work of these faculty-entrepreneurs.

We hope you enjoy this new expansion of the magazine.—JW

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



Mounting an Attack on a Furtive Form of Plaque

Everybody knows by now that arterial plaques are bad. These fatty deposits in blood vessels that feed the heart can turn deadly when they grow large enough to obstruct blood flow to the heart, brain or other organs.

But not all plaques are created equal, and it turns out that the ones you can see aren't even the most dangerous kind. In what's no less than a major breakthrough in the field of cardiology, researchers in the past half-dozen years have found that the most nefarious plaques lurk inside the artery wall. These soft, silent killers, it turns out, are responsible for the vast majority of fatal heart attacks.

"Sadly, it's not that uncommon a story. A fit man in his 40s or 50s goes in for his annual check-up and gets a clean bill of health from his doctor. He leaves the office, his heart ticking along like a fine, Swiss watch. He goes home and within a few days—or even hours—he drops dead of a heart attack."

This scenario comes from UK's Robert Lodder in the College of Pharmacy, who has spent nearly 20 years studying plaque's role in heart attack and stroke. Recently, the Cincinnati native has been among those researchers doing pioneering work in characterizing this more silent-but-deadly form of plaque attack.

"We call these 'vulnerable plaques.' They're small with a soft lipid core, nearly fluid, covered by a thin, fibrous cap of protein," Lodder explains. (Lipids are the main structural components of living cells and include fats and waxes.) "As the heart beats, the arteries and plaques move, so these plaques are in constant motion, and force is exerted on

Robert Lodder's fiber-optic catheter, which was patented in 1996, tours the coronary arteries looking for large spectral signatures of cholesterol. If it encounters these signals, the computer marks the spot as a vulnerable plaque.

the edges of the fibrous cap covering the liquid pool." Even a small tear in that cap lets a little content ooze out into blood vessels. Unfortunately, the leaked lipids quickly produce a clot, and within 60 to 90 seconds the clot occludes the whole vessel. "The result is quick: you die," Lodder says.

Once it started becoming clear to researchers and cardiologists that these sneakier plaques were causing the vast majority of fatal heart attacks—some researchers believe up to 70 percent of heart attacks are from vulnerable plaques—Lodder began to think about how best to seek and find sites where these plaques gather and bide their time. His thinking led him to bring together two unlikely partners in this seek-and-find mission—fiber optics and mathematics.

"We've known for a while that different tissues demonstrate unique spectral properties when reflected light from these tissues is measured," Lodder explains. "These properties can be used to discriminate between healthy and diseased tissue. Recent advances in the telecommunications industry have produced cost-effective, fiber-optic light sources and detection devices to send and measure light, and we can now use this technology in medicine."

Incorporating such knowledge from clinical research, Lodder developed algorithms that correlate reflected tissue signals to known patterns, producing diagnostic devices that can determine the presence and progression of diseased tissue. He patented the algorithm, used to reconstruct infrared images of this plaque, in 1995. But he didn't stop there.

"First-stage immediate treatment is important, of course, for someone having a heart attack who's brought into

the emergency room," says Lodder, "and there are wonderful advances, like angioplasty and stenting, for such a patient. But now we know it's important to go further. We want to make a map of the rest of the coronary tree—all the sites that haven't just been treated—and predict where and when the next heart attack will occur so that it can be prevented."

In order to make this map, Lodder needed to design a probe to do on-site inspections. So he developed a fiber-optic catheter, which was patented in 1996, to do exactly that.

The experimental procedure begins with a heart-attack patient who has just had an occluded artery opened. Lodder's catheter, which is about 3½-feet long and hooked to a computer, is inserted into the system of coronary arteries. The probe is directed to the heart and tours the entire neighborhood of vessels, sending near-infrared signals to the computer. The probe looks for large spectral signatures of cholesterol, and if it encounters these signals, the computer marks the spot as a vulnerable plaque.

"The physician sees this all on a screen," Lodder says, "so he or she can mark the identified spots on a patient's chart. Ultimately, the goal is to pinpoint the most vulnerable spots—those with the biggest lipid mass and the thinnest cap—and then predict which ones are going to lead to a heart attack and how soon."

Lodder knew this was big, and so did James Muller, then director of the Gill Heart Institute at UK. "The more we talked, the more we became convinced we needed to form a company to begin to market this technology," says Lodder. Original seed money for the company, which they called InfraReDx, came from

a couple of Lexington investors, including the late Hilary Boone, a UK alum and well-known philanthropist. Additional funding came from the NIH.

Founded in 1998 and now headquartered in Cambridge, Massachusetts, with Muller as the company's chairman (he left for Harvard last year), InfraReDx has focused on continuing to develop the near-infrared technology to detect and treat diseased tissues, and to develop ties with manufacturers and distributors of medical devices.

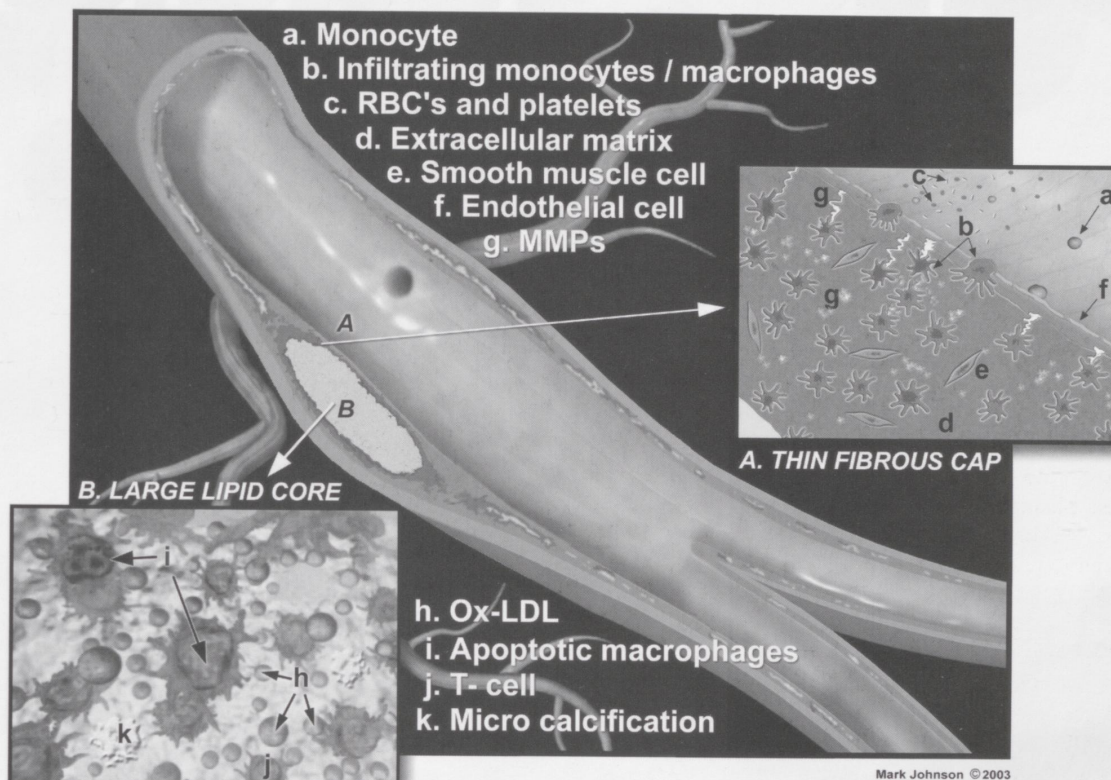
Although only a stockholder in the company now, Lodder is continuing to do his part to further the company's prospects. In 2002 he published an article on the efficacy of this technique in *Circulation*, the top journal in the field of heart-disease research. "I hope the article continues to help the company establish the legitimacy of this technique," Lodder says. "It'd be great if more people realized it was worth investing in."

Company representatives from InfraReDx are making more and more cardiologists aware of this potentially life-saving equipment, and physicians are now using it as part of a Phase I clinical trial. In this early-stage trial, small numbers of people undergo the procedure so that its efficacy and safety can be determined. The equipment and the procedure continue to work as designed, Lodder says, but there is a downside to doing such a trial.

"It's very, very expensive. Because the computer and the laser system that powers it are not proven devices, we have to give them away to the physician," says Lodder. "Also, we have to pay all the patient's medical expenses."

InfraReDx reps are also talking with several drug companies, Lodder says, so that this technology can be coupled

Vulnerable plaques are characterized by a soft lipid core (B), covered by a thin, fibrous cap of protein (A). As the heart beats, force is exerted on the cap. Even a small tear in that cap lets a little content ooze out into blood vessels. The leaked lipids quickly produce a clot, and within 60 to 90 seconds the clot occludes the whole vessel. "The result," Lodder says, "is quick: you die."



with targeted drug therapy. "It's one thing to tell a patient, 'Oh, I found this place in your blood vessel, and in less than a year you're going to have a fatal heart attack.' Well, this is obviously not as helpful as saying, 'Not only have I found this spot, I also have the perfect drug to keep you from having that heart attack.'" Right now, Lodder says, only a few drugs are available that can regress vulnerable plaque, but drug companies are in an all-out scramble to develop effective drugs as quickly as possible.

Developing this technology and seeing it work under the guidance of a physician is just one professional satisfaction among many for Lodder, who even as a kid knew he wanted to become a scientist. "Before I was in kindergarten I used to build labs on our dining room chairs, assembling just about any kind of gadget I could find," he says.

"I'd watch all the space launches and couldn't decide whether to be an astronaut or a scientist." His father convinced him that the odds of becoming an astronaut were daunting, so Lodder traveled the path of the scientist. He won't ever explore Outer Space firsthand, but his inner-space explorations may just lead to the saving of thousands of lives. ■

More faculty entrepreneur stories can be found at www.rgs.uky.edu/ca/odyssey/exclusive.

Domestic Violence:

Fighting Back

WRITTEN BY
Robin Roenker



Part of the research team (from front left and around): Karen Medley, Amy Wells, Kelli Frakes, Candice Burnette, TK Logan, Lisa Shannon, Janet Price, and Jennifer Cole.

"He attacked me with a pair of scissors and held me in the apartment all weekend, physically and verbally abusing me the whole time. On Sunday, I told him I was taking out the garbage; instead, I went to the hospital."

"He was drunk. He tried to break my leg, tried to stab me with a knife, slapped me, pushed me up against the wall. When he pushed me off the porch, I ran away and went to the police station."

"He'd call me all the time when he was drunk, at all hours of the day or night. He threatened to kill me and burn the house down, and this escalated over time."

These scary and sad stories all end with a common line: "Then I got a protective order."

A woman
is a victim
of a
violent
crime
by an
intimate
or former
intimate
once every
36
seconds.

[source:
Bureau of Justice]

"It's women's stories of pain and courage that motivate me to do the work that I do," says TK Logan, an associate professor in the Department of Behavioral Science. "I see remarkable strength in these women who face the fear of what the men in their lives might do to them, especially after the women leave and get a protective order. I really admire the courage of these women."

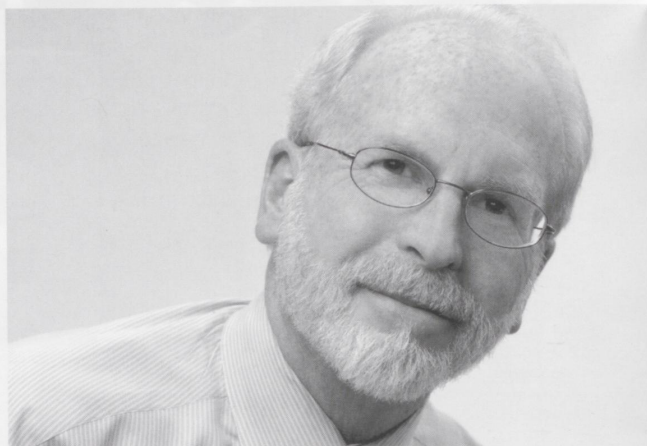
In a project titled "Alcohol, Violence, and Health Services in Rural Women," Logan and her research team are taking a close look at women's experiences of domestic violence, the contextual factors involved, and how women cope with this adversity on a day-to-day basis.

The study is examining a broad range of health and mental health issues associated with domestic violence and is one of more than 20 projects under way at the University of Kentucky Center on Drug and Alcohol Research (CDAR). Co-investigators in this study are Robert Walker, who joined the center as an assistant professor in 1999, and Carl Leukefeld, who established the center in 1990 and serves as CDAR director and chairman of the Department of Behavioral Science. The project began in September 2000 and is funded through 2005 by a \$2.2 million grant from the NIH National Institute on Alcohol Abuse and Alcoholism.

Women's stories are the heart of this time-intensive and ambitious study. At the outset, project staff planned to interview 750 female victims of domestic violence, asking them to share important aspects of their lives including their health, mental health and use of substances in coping with stress.

One of the unique features of this study is that each participant has obtained a protective order in a Kentucky court in hopes of putting an end to the violence she faces at home. Previous studies of domestic violence victims have focused on women who have spent time in abuse shelters or who are in mental health or other medical treatment settings. "Using a protective order sample allows the research team to learn about the experiences of a broader range of women—both those who do and do not seek formal health or mental health services after victimization," says Logan. "It also gives us the opportunity to talk to women with a wide range of victimization experiences."

This study is also unique in that it includes rural and urban women. "This is one of the most important aspects of the project. We want to see if there are differences in the ways the two groups experience domestic violence," says Leukefeld.



"Protective orders might work," says Robert Walker, who has worked in Lexington for 27 years as a mental health center director. "We'll be the first group to look at this issue in rural and urban settings to see what happens to women after they get a protective order."

Do Protective Orders Work?

One central question the team hopes to answer is a basic yet crucial one: Are protective orders doing their job?

"The overwhelming majority of states have protective orders," says Walker, a Berea, Kentucky, native who has worked in Lexington for 27 years as a mental health center director. "Legislators passed these laws with the assumption that the orders would provide some protection for victims of violence. Protective orders might work. No one really knows the answer to that question. We'll be the first group to look at this issue in rural and urban settings to see what happens to women after they get a protective order."

The team's findings regarding the effectiveness of protective orders will be very important for policy makers, says Walker, who adds that his years of front-line exposure to the negative physical and mental outcomes of abuse motivate his efforts to better understand domestic violence and develop ways to counter it. "We hope we find in this study that a substantial percentage of women who get the protective order report less violence afterward—that would be wonderful," he says.

The University of Kentucky Center on Drug and Alcohol Research

All too often, though, the opposite is the case. Many times violence continues after the order is issued, at least for a while. In addition, many women face a multitude of barriers in trying to stop the violence and in trying to leave their abuser. Sometimes children are a consideration; other times, the women simply feel they have nowhere else to go. "And obstacles to stopping the violence and leaving an abusive

To help participants answer such a sweeping and specific battery of questions, the interviewer uses a "calendar" technique. Respondents use anchor dates—birthdays, holidays, and so forth—as triggers to help them remember instances of health problems, periods of depression, incidents of violence, drug use, as well as trips to the doctor and other significant events.

Each year nearly 28,000 temporary protective orders and more than 18,000 emergency protective orders are issued in Kentucky. [source: Kentucky State Police]

relationship may be even more overwhelming for domestic violence victims in rural areas than for those in urban areas," Logan says. "There are victims living in isolated rural settings where the economy is in terrible shape."

"Some of these women are so tied to their partner or their spouse economically and in terms of social pressures that it is difficult to break away from that," says Leukefeld. "It's a reality. And it's a reality that's different in a rural area versus urban settings. This difference is what we're trying to understand."

Getting Personal

Participants in the study take part in a three- to four-hour baseline interview as well as a two- to three-hour follow-up interview 12 months later. The interviewers ask specific questions about the types and amount of physical and emotional abuse the women experience. For example, rather than asking merely *if* the women had been threatened by an intimate partner, the interviewer asks them to describe *how* the threat occurred. Was it verbal? Were weapons involved?

Working to elicit the same degree of detail, interviewers pose other questions to get a sense of the women's overall physical and mental health. Participants are asked how many days in the past month they experienced emotional distress, how many times in the past year they sought health care, how often and when they used alcohol or other drugs.

History of victimization. Quality of sleep. Symptoms of chronic pain. Existence of support networks. Stressful life events. Relationships with others. Barriers to seeking health and legal services. It's all covered.

"We can see whether doctors' visits increase or decrease over time. Does she tend to hide after periods of severe violence, or seek treatment? We get month-by-month pictures of the participant's victimization and her substance abuse," says Logan. "And based on this approach, we can ask other questions: When there's more severe violence, does substance abuse increase before or after that violence, or do patterns pretty much remain the same regardless of levels of violence?"

Also, drawing on the participants' experiences, the team hopes to determine to what degree alcohol and drug abuse is related to coping, if substance use is a risk factor itself, or if both of the above are true, Walker says.

Although the stories they tell focus on abuse, sometimes severe, for many of these women, the interview is a positive experience. "They tell us they appreciate that we respect them enough to want to hear their stories," says Logan.

Is Domestic Violence Different in Rural Areas?

Leukefeld returns to the central focus of the project: the differences between the experiences of rural and urban domestic violence victims. In fact, the impetus for the grant, he says, sprang from the team's belief that women's experiences of victimization were going to be very different in Eastern Kentucky. "One of our research goals," he says, "is to see if this belief is supported by the data." Half of the study participants are domestic violence victims from Fayette County, which includes Lexington, and half are from rural areas of Eastern Kentucky, predominantly Floyd, Letcher and Perry counties.

Though the team is still conducting interviews and only preliminary data are available, results so far have confirmed many of the researchers' expectations: Domestic violence appears to be different in rural and urban areas, and many times it's the rural women who face more severe circumstances.

"Women in rural areas are more likely to be married to their partner than women in an urban area," Logan says.

are not reporting that as often in the urban area," Logan says, adding that more women in the rural areas report threats in general, and specifically threats with weapons, than women in the urban area.

Findings so far also suggest that rural women have more trouble getting a protective order. "You're not supposed to be charged a fee for protective orders, but they do that in some rural counties," Logan says. "And in some places they

Nearly one in three adult women experience at least one physical assault by a partner during adulthood. [source: American Psychological Association]

"And rural women tend to have been with the perpetrator longer—on average 10 years versus five years among urban women."

To date, the study has uncovered no significant differences in the rate at which rural and urban domestic violence victims are accessing health services—one of the important findings so far, Logan says. Still, rural domestic violence victims tend to report poorer overall health. For example, preliminary findings show that while rural women experienced medical problems an average of 9.5 days in the month prior to the follow-up interview, urban women reported similar problems an average of 6.5 days. "What's the connection between this higher incidence of medical problems and domestic violence?" Logan says. "That's what we're working to find out."

Patterns of sleep are also different for the two groups. "Rural women get less sleep," Walker says. "Does this finding reflect a higher level of fear or guardedness in the home environment? Possibly. Does it represent fear related to the perception of less protection from law enforcement? Possibly. We're going to need more time to see. But there's something going on there."

In looking at the two groups' alcohol and drug use, the research team has noticed another difference. "More rural women are using prescription drugs than urban women are, while more urban women are using alcohol and illegal substances," Logan says.

There also seem to be notable differences in the kinds of violence that occurs in the two areas, Logan says. For example, one in four of the victims from rural areas report that her partner has tried to hit or run her over with a car. "Women

publish the women's names in the local papers, which may not only create more stigma for victims but also serve as a barrier to obtaining a protective order. You have to be very determined to get a protective order in some rural areas."

Working to Make Home a Safer Place

Though trying to probe so many issues involved in domestic violence might seem overwhelming, for Walker it's the complexity of this project that makes it so exciting.

"There's a huge wealth of variables being collected here. Mental health, physical health, substance use. Any one of those could have been the focus of a study, but this one's got them all," Walker says. "It has so many avenues for rethinking how we understand those problems for women."

"I've always been interested in rural life—its rewards and challenges," Leukefeld says. "I grew up in a small town north of Chicago and worked 23 years in the health service there, but I always wanted to get back to a rural setting." Part of the appeal of the University of Kentucky at that point in his life was Kentucky's large, rural population and the opportunity to interact with this group.

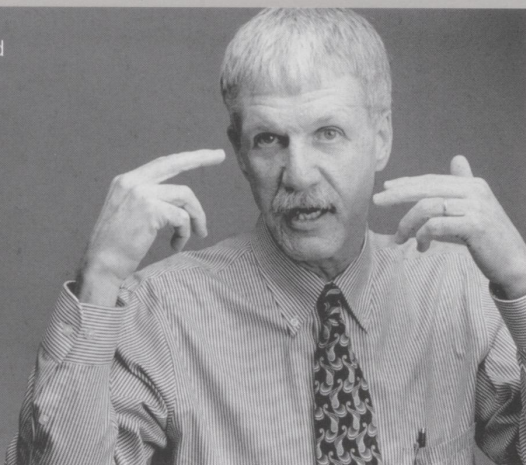
"As a researcher, I feel a great passion about this line of inquiry. There is so much about domestic violence that we do not know and this study gives us an opportunity to examine it in great detail with people who experience it every day," Logan says. "I hope that we can contribute to women's safety in the long run by doing this study. That's reason enough to do this work." ■

The University of Kentucky Center on Drug and Alcohol Research

When Carl Leukefeld left the National Institute on Drug Abuse in 1990 to establish the Center on Drug and Alcohol Research (CDAR) at the University of Kentucky, two things influenced his change of address: Kentucky's large rural population was one strong appeal; another was UK's longstanding reputation as an authority in addiction research.

Today, CDAR's research into the biological, psychological and clinical aspects of drug abuse builds on and continues the university's legacy of leadership in the field, employing about 115 staff members and bringing in an average of \$6.5 million in research funding annually from

Carl Leukefeld



federal, state and local sponsors.

"We focus on drug abuse in all its aspects—services, epidemiology, treatment interventions," says Leukefeld, who is a professor of psychiatry, behavioral sciences, oral health sciences, and social work at UK in addition to his role as CDAR director.

Currently, CDAR researchers are at work on 24 research projects, on topics ranging from managing a database of statewide DUI cases for the Kentucky Division of Substance Abuse, to examining the substance-abuse treatment needs of fathers who have failed to pay child support, to gathering data on treatment outcomes of everybody in Kentucky who seeks drug-abuse treatment through publicly funded treatment programs.

Though many programs are state-supported, the National Institutes of Health (NIH) is the primary source of funds for much of the center's research, Leukefeld says. In addition to the "Alcohol, Violence, and Health Services in Rural Women" grant supported by the National Institute on Alcohol Abuse and Alcoholism, the NIH funds center research on employment intervention for defendants in the drug court system, analysis of drug abuse treatment success rates of Kentucky prisoners, and a study to reduce probationers' behaviors related to HIV. In addition, last fall CDAR was awarded one of seven NIH grants nationally to establish a center to improve transition interventions for addicted inmates moving from the criminal justice system back into communities.

One of the center's largest projects is its Institute on Women and Substance Abuse, begun in 1993. The institute's goals are service-focused. It operates as a state and national resource center, working primarily to increase the number of women served in publicly funded drug- and alcohol-treatment programs across the state.

Through the Institute on Women and Substance Abuse and research like the "Alcohol, Violence, and Health Services in Rural Women" project, a significant portion of the center's work is focused on women's health as it relates to substance abuse.

For Leukefeld, that's no accident.

"I have always focused on women's issues," he says. "One of my interests is in people who are less-served or underprivileged. With drug abuse, women are always the ones who get the worst end of the deal. They're always the ones who get sucked in by somebody, usually a guy, who says, 'I want to establish a relationship with you, and by the way, I'm a drug user.'"

With the variety of projects CDAR encompasses, Leukefeld believes the center's work will have lasting impacts on the health of citizens across the state—men and women, drug users and, indirectly, non-users too.

"We're trying to develop knowledge so that we might upgrade the services and health of all people in Kentucky," he says.

The University of Kentucky
Center on Drug and Alcohol Research



Photo: Alicia P. Gregory

Research Outreach

W R I T T E N B Y
A l i c i a P . G r e g o r y

The sound of Lee Sexton's banjo bounces from the hand-hewn ceiling beams to the original plank floor, masking the crash of thunder outside. The dancers weave back and forth, looping arms as they switch partners. The bystanders, like me, make paper fans in the sweltering meeting room that, despite the rain, hasn't gotten any cooler since this muggy July day topped 90 degrees.

Before the dancing began, Blackey, Kentucky, native Charlie Whitaker addressed the group. He painted a picture of other summer nights in Eastern Kentucky: furniture was put out in the front yard, cleared from the main room to accommodate as many neighbors as could squeeze in. The dancing would go on till the sun came up. "You know, it just wasn't safe to travel back home at night through these mountains," says Whitaker, the square-dance caller for the Carcassone Community Dancers.

Ranging in age from 17 to 75, the dancers are members of one of the nation's oldest community square dances, and their sashays, promenades and do-si-dos preserve the traditional dances their ancestors brought with them when they settled in Eastern Kentucky.

This is history in motion, the kind of thing passed from generation to

UK partners
with Kentucky
teachers to
bring history
to life

American Legacies



David McFadden teaches arts & humanities and band at North Laurel High School, and has 10 years' teaching experience. He says, "I see a lot of possibilities for using simulations in my classes. I especially liked the Native American culture things we've learned this week, and that's part of our core content for high school arts & humanities assessment. I've got a better understanding of how to wrap history into my classes."

generation that rarely makes it into history books. But as I watch the faces of the 20 public school teachers who join in with the Carcassone Dancers, I see the virtue in preserving these traditions and teaching children, by tangible means, how to discover and value the past.

And that's why we've all come to Pine Mountain Settlement School in Harlan County. I'm here to record the experience of American Legacies, a three-year professional development program for history teachers. And, thankfully, the teachers don't seem to mind an outsider. In fact, other than the telltale accent I haven't been able to shake in the 11 years since I left my native Detroit, I seem to fit in.

But this isn't about me. It's about changing the way kids relate to history. American Legacies combines new historical scholarship and creative ideas, including children's literature and simulations in which kids research and portray people in an historical event. The program's focus is on crafting curriculum for elementary, middle school and high school classrooms that centers on investigating the past from multiple perspectives to help students think historically—to grasp the complexity surrounding historical figures and events.

Twenty teachers from eight Kentucky counties (Bell, Clay, Harlan, Knox, Jackson, Laurel, Rockcastle, and Whitley) became American Legacies Fellows in this program funded by a three-year, \$942,000 grant from the U.S. Department of Education's Teaching American History Program.

American Legacies brings training to where these teachers live, instead of making them travel three or more hours

to Lexington, Frankfort or Louisville. It's a different approach from traditional professional development programs, Project Director Rebecca Hanly from the Kentucky Historical Society tells me. She visited 15 school districts in a targeted effort to recruit applicants. Teachers were required to apply for the program, which offers benefits including free books and teaching materials, travel expenses, graduate credit, a \$500 yearly stipend, in-class assistance and mentoring, the chance to visit historic sites across the state, and interaction with university scholars.

American Legacies fellows attend fall and spring two-day seminars and a week-long summer institute for the three-year term, and will create grade-specific teaching units that can be shared with other teachers across Kentucky.

Hanly points out two ways this program is unique. First, American Legacies was born from the vision of people across Kentucky: Harlan Independent Schools applied for the grant in partnership with the University of Kentucky, the Kentucky Historical Society, the Kentucky Department of Education, the Kentucky Heritage Council, and the Kentucky Virtual University.

Second, the program curriculum is tailored to Eastern Kentucky. Most of the 114 school districts nationwide that received these grants chose to buy pre-packaged curricula. "We didn't," says Kathi Kern, who with UK colleague Linda Levstik is shaping the content for American Legacies. "We're trying to stress American history content, wrap it with teaching methods and have a regional focus."

"Eastern Kentucky has an enormously rich store of history that doesn't always get tapped. So part of what we're trying

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to do is make sure that local history gets embedded in a national context, and that national events are also seen in terms of their local impact," says Levstik, a professor in the UK curriculum and instruction department since 1982, and co-author of the book *Doing History: Investigating with Children in Elementary and Middle School*.

"Last year I worked with fifth graders on an archeology project, and one of the questions we asked them at the end was, 'What is the difference between archeology and history?'" says Levstik. "They said, 'Archeology is like fitting together a puzzle—you piece all these things together to try to figure out what happened. History is a story that's already been told—it's finished.' We want to get kids to see history in the way they see archeology—as unfinished stories."

Levstik continues, "If you can get kids to start with a question, they're more likely to really get into the investigation."

She details the steps of this investigation. It starts with primary sources—newspapers, magazines, journals, letters, and photographs from the time period—and then incorporates secondary sources such as films or documentaries and history-book interpretations of an event. The next step is thinking about historical perspective—how does the worldview of the person who recorded these events influence the way we need to think about them?

Kern, who has spent 14 years at UK and whose research on the women's rights movement led to her 2001 book *Mrs. Stanton's Bible*, uses methods in her classroom that are a far cry from stale lecture-based curriculum. "We do simulations," she says, which are orga-

Linda Levstik (left) and Kathi Kern want their students to investigate history and, through interactive simulations, to reexperience it.





Melissa Singleton, an eighth-grade social studies teacher who's been at Rockcastle Middle School for 10 years, says she thinks it's important for kids to study their own families. "My father is from Ohio and my mom's from Kentucky," she says. "One of the things that I think is funny is we go north and they make fun of the way we talk, but my family in the north loves Bluegrass music and will happily get out there and dance to someone singing just the way that I talk. Kids need to learn to be proud, not ashamed, of where they grew up."

nized around an event, for example, a congressional debate, courtroom drama or a political rally. Some students, based on their research, portray historical people (they interact with the other characters in an event), and others serve as journalists or historians (they write and ask questions of the characters).

Kern explains, "Our approach is about teaching kids, and adults, that history is not signed, sealed and delivered—that it is open to debate and interpretation. The simulations rekindle important historical debates, so students can see that there was conflict as well as consensus in the past. As teachers, we can then make the analogy between the debates we simulate in the classroom and historical interpretation: whose perspective most influenced the historical narratives? Why do some perspectives seem to carry more weight?"

Kern, an associate professor, teaches American History 109 at UK to 300 students each semester, and uses simulations as part of her interactive curriculum. "I might do six simulations a semester, but there's a lot of activity around that." She uses books, films and lectures to set the stage for a simulation and act as bridges between historical events.

For about 90 percent of her students, Kern says, history comes alive. But she pauses and shrugs as she tells me, "I have about 10 percent who say this is a bastardization of what they believe history to be. Sometimes I'll even have resistance from some very good students because they've thrived in that traditional pedagogical model where the professor spews out information and the students write it down, absorb it and regurgitate it.

"What I try to stress to students is that you learn more when you're having fun and when you're engaged. Cramming for tests is not the way to learn—because there's a limited amount that any of us can memorize, but we can all develop our analytical skills and scaffold new knowledge onto things we already know and understand."

She tells me the way you shape a simulation is key: "I would never do a simulation where the traditional voices were muted in some way. You've got to have those power dynamics there." Kern says, with greater animation, "You can't just say, 'Here's an alternative fantasy version of history where everything's fair and just.'"

"When I do simulations, I always have time at the end for debrief. Say, someone had to portray a Ku Klux Klansman. They need a moment to say, 'Although I'm a white person and I portrayed this person, I don't agree with the KKK.'"

"Now, of course, this is different with children. You can't have a child portray Hitler. But I ask older students to suspend their own moral judgments about these people and try to figure out what made them tick. What was their vision of the world? What mattered to them? Why did they make the choices they did?"

Kern, a northerner like me (she's from Pennsylvania), says, "When I came to Kentucky and wanted to teach civil rights, I found some of my white students here weren't all that sympathetic, and that's when I realized I needed to learn the history of *these* people. Now I talk about the strife between coal miners—black and white—and mining company owners. Students who can resonate with that history are then more sympathetic when we get to civil rights

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Associate Professor of History Ron Eller says this picture of a flatboat on the Kentucky River is an example of how photographs can contradict historical myths, such as Appalachian isolation. Note the KSC shirt on the man off to the left. That stands for Kentucky State College—the predecessor of UK. “The dress of the passengers, including the KSC shirt on the one young man, speaks to the interaction between the mountain region and the Blue Grass,” he says.

and struggles of black people in America."

Kern sums up her goals for the American Legacies program: "On the one hand, we want to deepen the teachers' content knowledge in American history by exposing them to the latest scholarship. That's part of it. But at the same time, we want to engage the teachers in the same spirit of inquiry that we hope they will adopt with their students. We want them to *do* history—to conduct research, to engage in historical analysis, and to teach American history in ways that actively involve their students in thinking historically."

And as I listened to the teachers' discussions and watched the documentaries at Pine Mountain, I began to see how thinking historically is connected to breaking down barriers of myth and stereotype.

The theme for the Sunday-through-Friday summer institute at Pine Mountain was "Shifting Frontiers" and included a field trip to Cumberland

Gap, small group projects, and film and book discussions about Native Americans, settlers from all over the world who came to Appalachia, and later migration out of the region.

Levstik tells me, "The American Frontier is surrounded in myths, and those myths have been created and used for a whole variety of purposes, historical and otherwise. We started by looking at the myths surrounding Native Americans—the way they are presented in film, children's literature, tourist attractions, newspapers, and magazines."

I reached Pine Mountain at lunch time on Thursday, along with invited speaker Ron Eller, an associate professor of history who began his 19th year at UK teaching southern and Appalachian history this fall. For 15 of those years, he served as director of the Appalachian Center at UK, but retired from administration to return to full-time teaching in 2000.

The post-lunch discussion, led by Eller, centered on the people of Appalachia—who have, like Native Ameri-

cans, been the subject of many myths. He touched on two: isolation and violence.

People in Appalachia were no less cut off from the world than people in other rural areas in Wisconsin, Michigan or Mississippi, he says. Eller showed a telling photograph of a group on a flatboat on the Kentucky River.

"This was a common form of transportation into and out of the region at that time and belies the supposed isolation," Eller says. One man, off to the left, is wearing a shirt with the letters KSC. That stands for Kentucky State College—the predecessor of UK. "The dress of the passengers, including the KSC shirt on the one young man, speaks to the interaction between the mountain region and the Blue Grass," he says.

I noticed about half of the people in the photo are brandishing weapons. "Like many photos of this period, the passengers are holding up their guns, similar to the staged photographs of the Hatfields and McCoys taken a decade earlier, to fit the emerging national imagery of Appalachia as an isolated, backward and violent place."

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We then settled in to watch "Long Journey Home," a 1987 documentary by Eastern Kentucky filmmaker Elizabeth Barrett. For me, this film was fascinating because it weaves together narration by Anndrena Belcher, a Scott County, Virginia, native whose family moved to Chicago when coal work dried up, stories from Italian, Hungarian and Yugoslavian immigrants, and interviews with African Americans who left Alabama for wage labor in the mines.

I knew that machines were replacing men at that time, but this documentary showed the emotion behind how "progress" put miners out of work. In 1922 the first Joy Loader was sold. This "cotton gin of coal mining" was a conveyor belt with mechanized arms, and it did the work of 100 men. Men lost their jobs, and because they lived in coal towns in company-owned houses, they had no place to stay.

Between 1940 and 1970, 3.3 million out-of-work miners and their families headed north, to Cleveland, Chicago and Detroit. But the city wasn't for everyone. Belcher says in the film, as she walks through the Chicago streets, her family didn't settle in to Chicago thinking it was home—the mountains were home.

She says, "I took the elevated train to school. Just careening around in that concrete and that metal I just always had the feeling that this was a crazy way to live. All that sound—it didn't feel real natural to me." Belcher eventually returned to the mountains, as a folk dance teacher, but her parents, Bill and Clara, stayed in Chicago.

Bill earned close to \$3 a day at his first city job, loading freight cars. It took a while to earn enough money to bring

his wife and two daughters north. The Belcher family, like many other families with deep roots in the mountains, trekked "down home" for holidays and one weekend every month. This experience was common to many families in Appalachia, including some of the American Legacies fellows.

In fact, the fourth- and fifth-grade teachers crafted a simulation, which they presented on the last day of the summer institute, around the real-life experience of teacher Bobbie Dixon's family. Dixon, whose experience paralleled the Belcher family's, and his team wrote a three-act skit. It opens with the dad, whose construction paper nametag read "Jack Morgan Dixon husband/father," telling his wife, son and daughter he's lost his job at the mine. He plans to go to Chicago, get a job and a place to live, then send for the family. Dixon and his team wrote a script that incorporated themes like the difficulty of adjusting to the city and the teasing the kids endured in school because of their accents.

After the skit, Dixon described how teachers could use this in their classroom. "You could have kids write the script themselves, choose parts, and act it out in front of the rest of the class," he says. "You could even have the kids gather stories about migration from their own families, and write skits around that."

Jennie Watkins, who played the wife in that skit, told me the day before as we ate lunch why she applied for American Legacies. "I'm always looking for innovative ways to engage kids, particularly at the fourth-grade level. These are nine- and 10-year-olds that do not handle a teacher up there talking the whole time, so this looked like a great



Renee Burdett, who teaches fifth grade at Roundstone Elementary in Rockcastle County, says, "The nice thing about this kind of experience is that we get to hear about how other people teach history, and, as a group, we get to learn together over the three years."

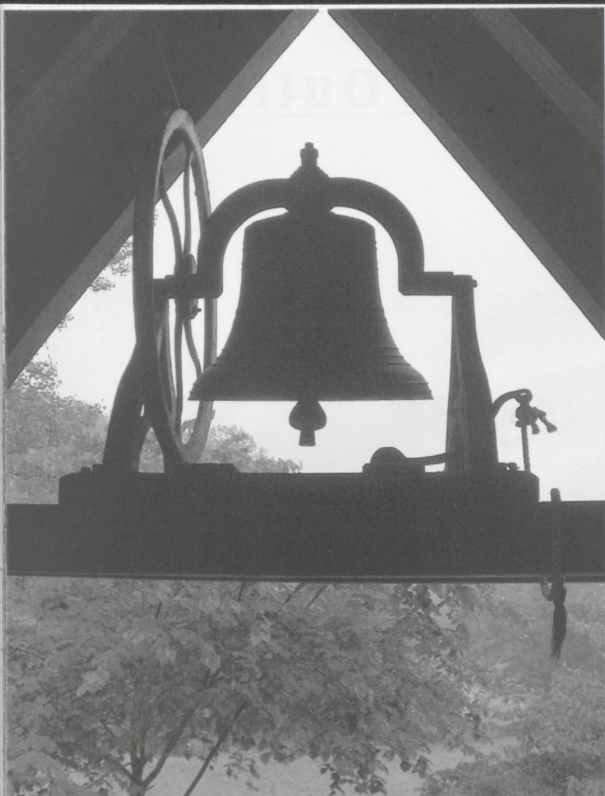


Photo: Alicia P. Gregory

Bobbie Dixon, a 21-year veteran teacher of fifth-grade social studies at Harlan Middle school, says, "After all these years, it's easy to become stagnant in the things we're doing in the classroom. This kind of professional development is something I think social studies teachers have asked for, for many years. Having these resources at our fingertips—these great films and books we've been talking about—is invaluable. We just don't have the time to go search for these things as we're developing lesson plans."

opportunity to get some hands-on activity and ideas about teaching."

The fellows will work on three projects—lesson plans that go along with the themes (shifting frontiers, democracy and conflict, and industrialization and reform) for each year. And helping them along the way is Sandy Stults, who serves as the program's master teacher.

Stults tells me how she got involved: "Rebecca Hanly told me about the program, and that they were working with the Harlan Independent School District. She wanted someone familiar with Eastern Kentucky and thought I would be that person since I grew up and taught in Letcher County. My roots go deep in the mountains.

"I had just retired from teaching when this opportunity arose. In 30 years of teaching, it is the most exciting program that I have been involved with," she says.

Stults, who the teachers affectionately named "Mom" during the summer institute, says, "My role is as a mentor to the teachers. My goal is to help the fellows achieve their goals in their classrooms."

Stults says she will serve as a resource person, team teach with some of the teachers, make sure their school administrators know what a wonderful job they are doing in the classroom and working with the American Legacies program, as well as find ways to showcase their projects within their communities and schools.

The goal of all of this, Levstik tells me, is to make history mean more to kids. "If we're going to teach history in schools, we need to understand why it's important. One, it makes us better citizens. If we're going to engage in a pluralist democracy, we need to know enough about each other to be able to speak intelligently to each other. Two, when we look through the past we learn something about what it means to be human," she says.

And after spending these two days with the teachers, I'm convinced, as Levstik and Kern are, that putting a face on the people of the past, whether it be through reading literature, watching movies or researching characters for a simulation, will better help children—the history makers of tomorrow—understand who they are and what their impact can be. ■

This program will have a sequel, American Legacies II, thanks to a new \$983,960 grant from the U.S. Department of Education Teaching American History Program. American Legacies Project Director Rebecca Hanly says, "There have been approximately 300 awards in this national program since 2001, and we're honored to be among the small group of those to receive a second award." This new award means that a second group of Eastern Kentucky history teachers will have the opportunity to get involved in this three-year professional development program that melds new scholarship with creative teaching strategies. For more information, visit http://history.ky.gov/Teachers/am_legacy.htm.

A Grassroots Approach to Medical Care

WRITTEN BY
Jeff Worley

Arthur is a diabetic. His doctor said he needs to exercise at least 30 minutes every day, but Arthur doesn't like to exercise so he doesn't. What he likes to do is sit and watch sports on TV, so he does. He typically eats a bag of potato chips as he lounges in his La-Z-Boy, and downs a few beers. He's 40 pounds overweight, and gaining. He's supposed to do finger sticks twice a day to check his blood-sugar level, but pricking the end of his finger is painful, so he often "forgets" to do it. Arthur is a worst-case scenario in self-management of diabetes.

"Once diagnosed, diabetics have to deal with several lifestyle changes all at once," says Kevin Pearce, the University of Kentucky's Michael Rankin Professor of Family Medicine. "It has been estimated that between 80 to 90 percent of type 2 diabetics don't manage their disease the way they're supposed to," he adds. Type 2 diabetes, sometimes called adult-onset diabetes, accounts for 90 to 95 percent of all diagnosed cases.

At the University of Kentucky, a team of researchers is tackling the problem of



Samuel Matheny (left),
Margaret Love and
Kevin Pearce

***In 2001
nearly 300,000
Kentuckians,
or 9.7 percent
of the adult
population, had
diabetes—
one-third
of them
undiagnosed
with the disease.***

diabetics' adherence to treatment in a novel way. Funded by a grant from the U.S. Public Health Service, Pearce is working with physician and researcher Samuel Matheny and researcher Margaret Love (all are in the UK Department of Family Practice and Community Medicine) on a trial that focuses on adults with type 2 diabetes mellitus who have uncontrolled hypertension, high blood cholesterol, or both.

How bad is the problem of diabetes in Kentucky? In 1994, diabetes in the commonwealth stood at the national norm, but by 2000 the disease had reached near epidemic proportions. And the prevalence of the disease in the Bluegrass state was among the highest in the nation. According to a recent study released by the University of Kentucky Center for Rural Health, diagnosed diabetes is 67 percent more prevalent in Kentucky today than it was in 1994. In 2001 nearly 300,000 Kentuckians, or 9.7 percent of the adult population, had diabetes—one-third of them undiagnosed with the disease.

The UK diabetes study is one of several under way as part of the Kentucky Ambulatory Network (KAN) program. KAN is a primary-care, practice-based research network established in 2000 by UK in cooperation with the University of Louisville and the Kentucky Academy of Family Physicians.

KAN currently includes 127 community-based physicians, nurse practitioners and physician assistants in 37 Kentucky counties, 36 family practice faculty, and 37 faculty in other fields from UK and the University of Louisville. The network is supported by federal grants from the U.S. Department of Health and Human Services.

"The novel part of this adherence trial," says Matheny, "is that we're testing the effectiveness of a support person—a relative or close friend—to 'intervene' to help the patient remember to take his medicine, keep doctor's appointments, improve eating habits, encourage regular exercise, and so forth. The intervention group in this study will include this close support; the control group will not. Our goal is simply to improve adherence to treatment for diabetics to reduce their cardiovascular risk."

"It'll be interesting to see if a partner's management helps a patient to be more regular in their treatments," says Jeffrey Fox, a physician in private practice at Central Baptist Hospital in Lexington. "If we find out there's a difference, we'll start recruiting more friends or relatives to help."

"This study is a good opportunity for those of us in private practice—who don't have funding to do research—to be a partner in answering important health questions," says Fox, who earned his medical degree from UK in 1980.

"And Dr. Pearce and the UK staff have made it easy for us to participate."

Matheny, who has served as chair of family practice since 1993, is clearly excited by what KAN can do. "It's a grassroots approach to both science and patient care," he says. "Its mission is to advance knowledge and to promote what are called 'best practices' at the primary-care level, through the study of common health problems."

An important aspect of the network is that these health problems are discussed and treated in the settings where people get most of their health care most of the time—in the primary-care physician's office. "We're taking this approach," Matheny says, "because we want to broadly represent primary-care practices in Kentucky and the patients they serve, many of whom are in rural communities."

"Sam got us off and running with this, and it's full-throttle now," says Pearce, who came to UK five years ago from the Wake Forest University School of Medicine. He adds that the program got off to a good start with a little help from their friends.

"First, we simply called our medical friends in Kentucky and told them about the research network we were building. We made an appointment to meet with them and talk about how they might participate in KAN."

"We emphasize the flexibility of the network," says Love, who has been a UK teacher and researcher since 1992. "We make it clear that participating clinicians can be as active as they like—they can propose studies, participate in studies, or both. We want to conduct research that matters to them."

In addition to the project on social support for diabetic patients, current

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Research Outreach

studies under way include screening for colon cancer, electronic information management, the prevalence of chlamydia (a sexually transmitted disease) among young adults in Kentucky, and barriers to medical treatments and services in the state.

One of Love's roles in this outreach effort is informational, she says. "I talk with UK researchers to let them know about the various KAN projects. It could be that the best way for researchers to get answers to the questions they have is to work with a practice-based network."

KAN's first major study, which began in 2001, replicated the National Ambulatory Medical Care Survey and added four items suggested by Kentucky physicians: tobacco use, obesity (as measured by height and weight), chronic pain, and depression/anxiety. This study involved 56 community-based clinicians who collected data from around 2,200 patient visits. The study focused on the demographics of patients, their reasons for visiting a doctor and the treatment they received.

Larry Fields, a physician in private practice in Ashland, Kentucky, participated in this study. "Because it's a broad-based approach, the research results are a lot more powerful," he says. "With so many investigators involved, there's now a great database available for us. I think this approach is going to be the way that practice-based research is conducted in the future," adds Fields, a graduate of the UK College of Medicine who has been in private practice for 20 years.

One value of the data generated from this study, Pearce says, is that primary-care physicians in Kentucky can now see how their diagnoses compare with

"The novel part of this adherence trial is that we're testing the effectiveness of a support person—a relative or close friend—to 'intervene' to help the patient remember to take his medicine, keep doctor's appointments, improve eating habits, and encourage regular exercise."

—Samuel Matheny

those of other physicians in the commonwealth and nationwide. Kentucky physicians can also zero-in on problems that should be targeted for more research at the primary-care level.

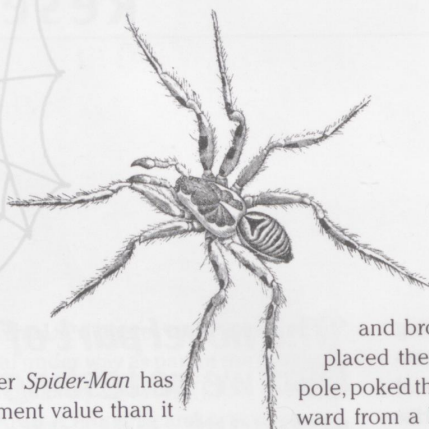
Forexample, although the three most common diagnoses in the KAN study—hypertension, respiratory infection and diabetes mellitus—are also among the most commonly diagnosed by doctors nationally, hypertension was the main reason for the patient's visit more often in Kentucky (7.8 percent versus 5.8 percent). These relatively high Kentucky stats didn't surprise Matheny.

"High blood pressure is a major risk factor in cardiovascular disease, which is the leading cause of death for all Kentuckians," he says. In 1999, 27.5 percent of Kentuckians had been told at some time by a doctor that they had high blood pressure. Other risk factors for cardiovascular disease include smoking, obesity, high cholesterol levels, and lack of physical activity.

Matheny says that individual primary-care physicians can benefit from results of this first KAN study in several ways. "One interesting finding was that among Kentucky physicians, depression or anxiety contributed to 17 per-

cent of KAN visits. So if a doctor realizes he hasn't seen these kinds of numbers in his practice, he might want to consider whether he's asking patients the right questions.

"In considering our contribution to this program, I like to think of UK as a university without walls," Matheny says. "I'm passionate about this opportunity to look at a set of health-related questions from practitioners of our state. The future of medicine will clearly be improved when a community of physicians is so committed to such a strong partnership."■



Tiny Spiders

Last year's blockbuster *Spider-Man* has much more entertainment value than it has scientific validity, but there's at least one scientific principle that holds true in the movie and in real life: if you're small, you can climb easier.

Admittedly, this principle may not be the reason behind Hollywood's decision to have a fairly short actor, Tobey Maguire, play the role of Spider-Man. However, it *is* the reason behind the success of a new theory published by UK spider researchers in the prestigious journal *Evolution*.

In an article titled "Climbing to Reach Females: Romeo Should Be Small," the scientists explain why male spiders of certain species are significantly smaller than their female counterparts. According to the researchers' "gravity hypothesis," smaller males have a physical advantage when they have to climb to find a mate. And the higher the females live, the smaller the males tend to be.

"It changes the whole picture of why males and females differ in size," says Jordi Moya-Laraño, a postdoctoral scholar in the entomology department. Moya-Laraño created the theory in collaboration with UK entomology professor David Wise and former postdoctoral scholar Juraj Halaj.

The prevailing explanation for size difference in male and female spiders—that females need to be a certain size to lay lots of eggs—gives only half the answer. The gravity hypothesis, explaining why males are small, is the flip side of the coin.

The researchers' gravity hypothesis not only caught the attention of *Evolution*, but also of *The New York Times*. "Publishing in a top journal is good, because your peers find out about your work," Moya-Laraño says. "But talking about science to the general public is important too. The *Times* article shows how catchy the idea is, and how understandable it is."

To test the theory, Moya-Laraño and entomology graduate student Cora Allard drove to a wooded area in Berea, Kentucky, collected several male and female spiders of the same species,

and brought them back to the lab. They placed the spiders, one by one, on top of a pole, poked them, and watched them glide downward from a line of silk they produced instinctively in response to the stimulus. The spiders climbed back up the pole naturally.

As the spiders climbed, Moya-Laraño and Allard timed their speed on a stopwatch, measured their climbing distance, and weighed them on a lab scale that is accurate to the one-hundred-thousandth gram. "If you remove the effect of weight—and you can do that statistically—the correlation between sex and speed doesn't hold anymore," Moya-Laraño says. "So that means the males are faster than the females *because* they are significantly smaller."

Though the gravity hypothesis wasn't a part of *Spider-Man*, Moya-Laraño still points out a correlation between the actor's size and his ability to scale buildings. "He's kind of a small guy—the actor," Moya-Laraño says. "To be Spider-Man, you need to be small."

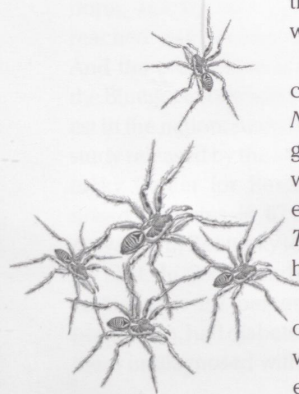
—David Wheeler

Untangling Alzheimer's Disease

At this moment, an estimated 4.5 million Americans have Alzheimer's disease. And by 2050, the Alzheimer's Association estimates between 11 and 16 million people will have the disease unless a cure or prevention is found.

Scientists studying Alzheimer's have identified several proteins that form tangles and knots in the brain; these abnormalities disrupt brain functioning. At UK, a team of scientists led by Guoying Bing, professor of anatomy and neurobiology, has gained important new knowledge about these tangles, findings that were published in a recent issue of *Nature*. The research group centered its work on the role of Pin1, a protein that acts on other proteins in the brain.

"This study may have found an important piece of the puzzle in Alzheimer's disease in that Pin1 may prevent proteins from becoming tangled—



therefore, increasing Pin1 function in the brain may be an effective way to treat Alzheimer's," Bing says.

The research team found a relationship between the amount of Pin1 and both the susceptibility of neurons to damage and the amount of protein tangles. They also found that mice with an artificial disruption of Pin1 develop a disease that resembles Alzheimer's, which means that Pin1 appears to have a role in preventing and protecting the brain from degeneration.

The study also suggests that a loss of Pin1 could contribute to other neurodegenerative diseases such as Parkinson's and Huntington's.

Record in Research Award Dollars

The University of Kentucky set another record in research grants and contracts with a fiscal year 2003 total of \$222.7 million. The majority of this funding was from federal agencies—\$131.1 million, or 58.9 percent of the total.

"The faculty and staff involved in our research enterprise should celebrate this outstanding achievement," says UK President Lee T. Todd Jr. Todd says this revenue is vital to the university as UK strives to become a leading research institution. "This is really a significant amount of money, given the economy and given some of the challenges that the university has faced with funding in the past few years."

"Faculty all across the campus are continuing—and expanding—their involvement in research," says Wendy Baldwin, executive vice president for research. "This is an exciting time for UK," she adds. "We look forward to seeing the results of our research efforts and the changes that they make in the lives of the citizens of the commonwealth and the nation."

**\$222.7
million**

2003

Groundwater Mystery Solved

You might think that abandoned animal feedlots are of little consequence to our environment and health. If so, you'd be wrong.

Researchers from the Kentucky Geological Survey and College of Agriculture at the University of Kentucky have identified such feedlots as a source of high concentrations of nitrate-nitrogen (nitrate-N) in rural groundwater supplies in Western Kentucky. Human sewage, livestock manure and chemical fertilizers are sources of nitrate-N contamination in groundwater.

Excessive levels of nitrate-N in drinking water can cause sickness in humans and livestock, and it's even possible to die from drinking water too high in nitrate-N. Infants less than 1 year old and pregnant women are particularly at risk.

Animals in feeding and holding lots create a compacted soil layer. The compaction, combined with swelling wet manure, usually prevents downward movement of nitrate-N to the water table. After the lot is abandoned, however, the manure and soil dehydrates and cracks over a period of years. And once surface cracks form, rainfall can move through the soil and transport nitrate-N to the water table.

So far, UK researchers have identified three abandoned lots as high-volume purveyors of ni-

trate-N, and nitrogen isotope samples indicate that the nitrate-N was derived from livestock manure. One of the three abandoned lots is located in Henderson County. The domestic water supply at this site contains 45 mg/L nitrate-N—four-and-a-half times the maximum contaminant level (MCL). The MCL established by the U.S. Environmental Protection Agency for nitrate-N is 10 milligrams per liter (mg/L).

Glynn Beck and James Dinger of the Kentucky Geological Survey, and John Grove and Eugenia Pena-Yewtukhiw of the UK College of Agriculture have devised a remedy. After doing geostatistical modeling of nitrate and organic matter data from more than 100 soil cores collected from abandoned lots, the researchers removed portions of the organic-rich soil from the lot and spread these on a nearby pasture. The excavated area was then backfilled with native soil and leveled.

The results to date are encouraging: the nitrate-N concentration in groundwater beneath the center of the feedlot continues to drop and is currently 118 mg/L, a considerable decrease from 145 mg/L prior to remediation one-and-a-half years ago. Prior to this project, very little research had been done to assess the impact of abandoned feeding and holding lots on the environment.

Trench Warfare

Mike Potter's new method of termite control is groundbreaking—in both senses of the word. His method involves digging up the ground around the perimeter of a termite-infested building. And his method is revolutionizing the termite-control industry.

Potter, former national technical director for Orkin and now a UK entomologist, works with homeowners, the pest-control and food-processing industries, and just about anybody else with a bug problem.

The pest-control industry is still relying on intrusive and expensive means to rid buildings of termites. Even after experts drill into walls and apply pesticides indoors, some customers are plagued by re-infestations months or years later.

But all that is beginning to change. A few years ago, new products were invented that are undetectable to termites and effectively lethal. Potter wondered if these liquid termiticides could work when applied primarily on the outside of a termite-infested building.

"My thoughts were: one, the termites can't detect it," he says. "Two, it transfers from termite to termite. Three, termites on the inside of buildings are usually connected to termites on the outside. They will continue to forage back and forth through the outside-treated soil. It would make sense that we could apply these products mainly around the exterior and solve the termite problem."

Potter calls the new approach to fighting termites "trench warfare," referring to the continuous four-inch trench dug around a termite-infested building. He began testing the concept in 1999.

The initial site was a tobacco barn in Paris, Kentucky. Potter and his colleagues created monitoring stations: plastic containers with the bottoms cut out that enclosed pieces of wood in the ground. Other stations, provisioned with cardboard, were mounted on termite-infested interior walls. Next, Potter's crew dug a shallow trench around the outside of the building and treated the soil with one of the new termiticides. The results were dramatic.

"Within a few months, all of the monitoring stations, including those on the interior, became inactive," Potter says. "When we opened up the stations, we found huge piles of dead termites as far as 15 feet inside the building. It was remarkable, because products in the past never had this kind of effect."

Since Potter has started sharing his research with the termite-control industry, thousands of houses in Kentucky and throughout the United States have been treated using the trench-warfare method—with equally impressive results. "This affirms that the minimally invasive method works in the real world and will be a great benefit to homeowners," Potter says.

Despite their enormous reputation as structural pests, much is still unknown about the organization and movements of subterranean termite colonies. "These are challenging creatures to study—you can't just lift the ground and observe their workings," says Potter. Which is where some "to-dye-for" research comes in.

"One method we termitologists use to trace termites' movements is called 'mark-recapture.' We add dyed paper to one of our monitoring stations. As termites eat the paper they ingest the dye, which colorizes their bodies [see photo on Contents Page]." By noting in which traps dyed termites reappear, researchers can track the movements of termites underground.

—David Wheeler



Dead termites packed inside a foraging tunnel in a crawl space under a house following an exterior termite treatment

Mare Reproduction Loss Syndrome: Update

In 2001, 30 percent of the pregnant mares in Kentucky aborted their foals, resulting in an estimated \$300 million blow to the thoroughbred industry. The mysterious illness, Mare Reproductive Loss Syndrome (MRLS), was initially linked to a peak population of Eastern tent caterpillars with a predilection for cherry leaves, which carry a precursor to cyanide. Because of UK research results in 2001 and 2002, many horse farms took preventative steps, chopping down cherry trees and muzzling mares to keep them from eating caterpillars.

The caterpillar-cyanide theory didn't hold up in early lab tests, but the caterpillar's role as the causative agent in the epidemic is clear. Bruce Webb (entomology), Karen McDowell (veterinary science), Neil Williams (Livestock Disease Diagnostic Center), and Merlin Lindeman (animal sciences) have conducted recent experiments that seem to indicate small hairs on the caterpillar's exoskeleton can partially penetrate the intestine, potentially resulting in abortion.

While MRLS losses have declined in the past two years, down to 12 percent in 2002 and much less than 1 percent in 2003, two teams of 15 scientists at UK are continuing work to reveal the mechanism by which ingested caterpillars cause mares to abort. For more, visit www.uky.edu/Agriculture/VetScience/mrls.

Selwitz Wins Major National Award

UK's Ada Sue Selwitz is the 2003 recipient of the National Council of University Administrators (NCURA) Award for Outstanding Achievement in Research Administration. Selwitz, past president of the Applied Research Ethics National Association, is currently director of UK's Office of Research Integrity. This office promotes ethical research conduct and educates faculty and staff on regulations involving human subject and ani-

mal research. NCURA's national honor is given to only one university administrator each year.

"I feel honored and thrilled to receive this award," says Selwitz. "But this is absolutely a 'shared award'—both in terms of the resources I've been given by UK and the people I work with here every day. Without this support, there's no way I could have made the contributions to research administration I'm being recognized for."

"Ada Sue is one of the top people in the country in the area of research integrity and compliance," says UK's Executive Vice President for Research Wendy Baldwin. "Her in-depth knowledge of federal policy and how that is translated into practice at the institutional level is remarkable."

"I really have a pretty straightforward philosophy about what I do and what I want our office here to do," says Selwitz. "Our duty is to promote research within the current ethical, legal and regulatory framework, and to shape the framework."

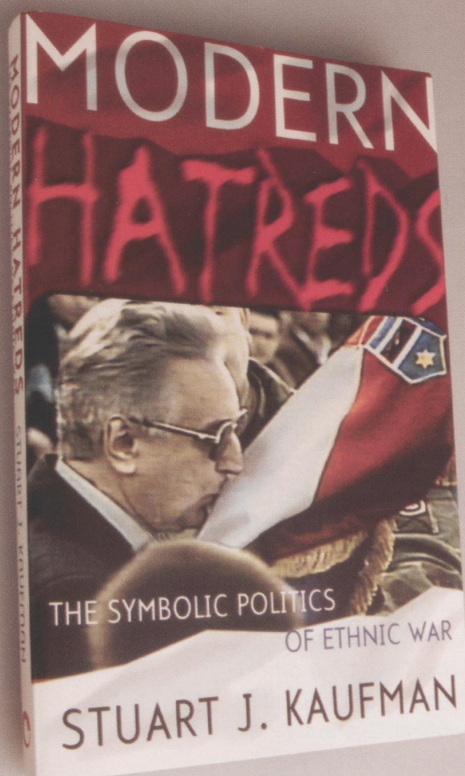
NCURA was founded in 1959 to protect the professional and academic rights of faculty and to keep them apprised of regulations, policies and procedures that affect the conduct of their research programs.

Ada Sue Selwitz



Book End

Modern Hatreds: The Symbolic Politics of Ethnic War,
by Stuart J. Kaufman,
Cornell University Press



"This isn't the book I intended to write," says Stuart Kaufman, motioning toward his copy of *Modern Hatreds*. "I started out to write a book about the various causes of ethnic war, but found myself focusing instead on the power of myth and symbol to stir up ethnic hatreds."

This was a significant shift, says Kaufman, a UK associate professor of political science who came to UK in 1990. "Basically instead of writing about how people think rationally about other ethnic groups, I began to look more at people's 'emotional beliefs.'"

The traditional way political scientists try to understand international conflicts, he says, starts with the premise that you can understand people's behavior by assuming they rationally calculate what their options are and then act accordingly. But rational choice doesn't adequately explain entrenched ethnic hatred and violence, Kaufman says.

What causes people to take part in some horrific war? How do leaders who want conflict convince ordinary citizens to join the army and risk their

Hate Thy Neighbor?

lives? To answer these questions, Kaufman says we need to look closely at the power of myth.

"In ethnic conflicts what's unique is that there's usually a specific outgroup that is already stereotyped. There's already a mythology in place that says you have to assume this group is hostile. Therefore, political leaders find it easy to get people to believe them when they say, 'They're going after us again. So we've got to attack first,'" Kaufman explains.

The problem is, he says, so many of these oft-repeated "histories" are simply untrue.

In 1389, Ottoman Turks clashed with Serb warriors in a bloody battle outside Kosovo, a fight the Turks eventually won. When ethnic conflict broke out between Serbs and ethnic Albanian Muslims in the early 1990s, Serbs cited the Battle of Kosovo as the starting point of 600 years of Muslim brutality and persecution.

"Serbs tell the story that they sacrificed themselves to save the rest of Christendom from being overrun by the Muslims," Kaufman says. "What they don't talk about is that just a few years later, in response to that battle, the Pope organized a crusade against the Turks. The turning point of this battle was when the Turkish army got reinforcements from Serbian cavalry. So it was the Serbs who helped the Turks against the Christians—the opposite of Serbian mythology that says they sacrificed themselves to defend Christianity."

If you look at a nation's relative lengths of good and bad relations with their ethnic neighbors, Kaufman says, myth again overpowers reason. "Let's say you have two ethnic groups that have shared a border for 400 years. Forty of those years involved terrible bloodshed between the two; 360 years were peaceful. What political leaders do is fasten on the 40-year period as 'typical' of the other group. The myth is so front-and-center in people's imaginations that they come to understand everything that happened before and after those 40 years in terms of the period of hostility."

So what can be done to lessen the power of these myths?

"First, you can change the acceptability of talking about the myths," Kaufman says. "In our country, for example, it's no longer acceptable to repeat stereotypical racist statements about blacks."

"The important thing is to try to make these attitudinal changes in different places simultaneously. Government leaders can promote more moderate attitudes at the same time school teachers do. It's crucial to get people to understand the 'other' as human beings with real problems rather than just some faceless enemy easily stereotyped as evil."

Kaufman's book won the 2002 University of Louisville Grawemeyer Award For Ideas Improving World Order. He will receive a total prize of \$200,000, some of which he will use, he says, to boost his 7-year-old son Sam's college fund.

—Jeff Worley

Odyssey
Fall 2003

Parting Shots

"History teaches us that men and nations behave wisely once they have exhausted all other alternatives."

—ABBA EBAN

"History is a closeout sale of new and old public myths."

—ANTON KAES

"Human history becomes more and more a race between education and catastrophe."

—H. G. WELLS

"History is the version of past events that people have decided to agree upon."

—NAPOLEON BONAPARTE

"People are trapped in history, and history is trapped in them."

—JAMES BALDWIN

"THERE IS NO HISTORY, ONLY FICTIONS OF VARYING DEGREES OF PLAUSIBILITY."

—VOLTAIRE

"We learn from history that we do not learn from history."

—HEGEL

"History will be kind to me for I intend to write it."

—SIR WINSTON CHURCHILL

"MORE THAN ANY TIME IN HISTORY MANKIND FACES A CROSSROADS. ONE PATH LEADS TO UTTER HOPELESSNESS AND DESPAIR, THE OTHER TO TOTAL EXTINCTION. LET US HOPE WE HAVE THE WISDOM TO CHOOSE CORRECTLY."

—WOODY ALLEN

"Political history is largely an account of mass violence and of the expenditure of vast resources to cope with mythical fears and hopes."

—MURRAY EDELMAN

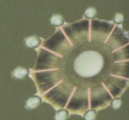
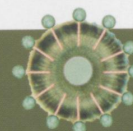
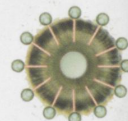
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