

University of Kentucky Research
Spring 2003

Odyssey

Clinical



A Human Safety Net
for New Drugs and Treatments

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Cover Story

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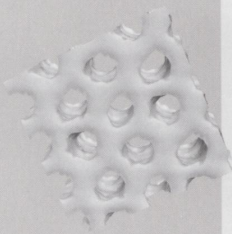
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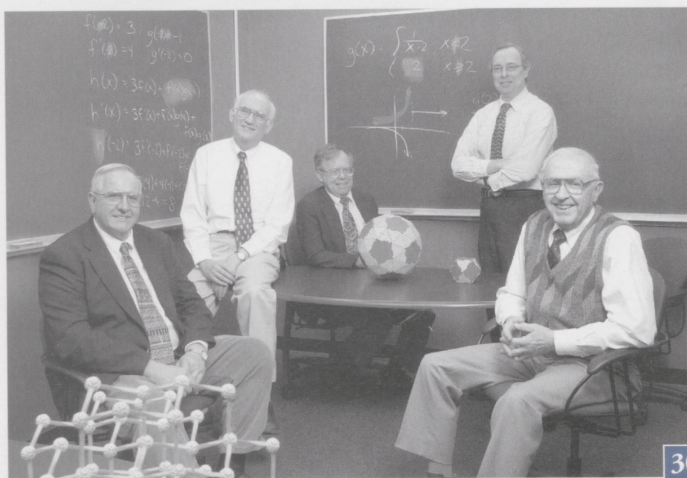
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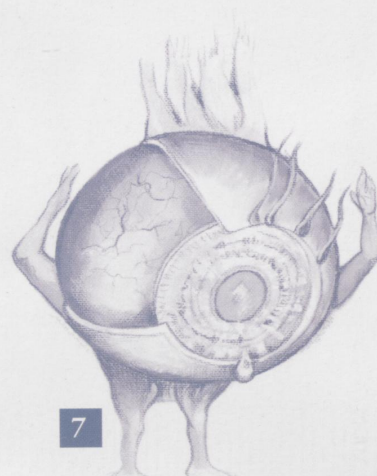
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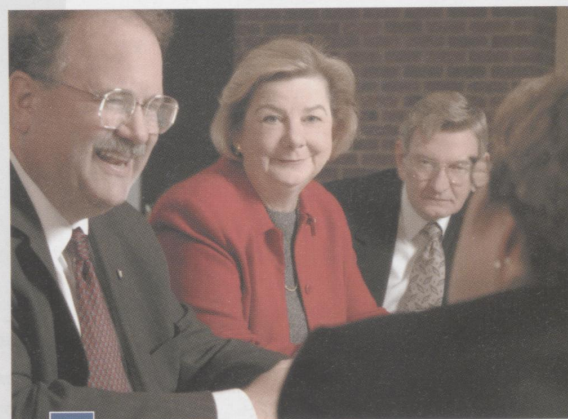
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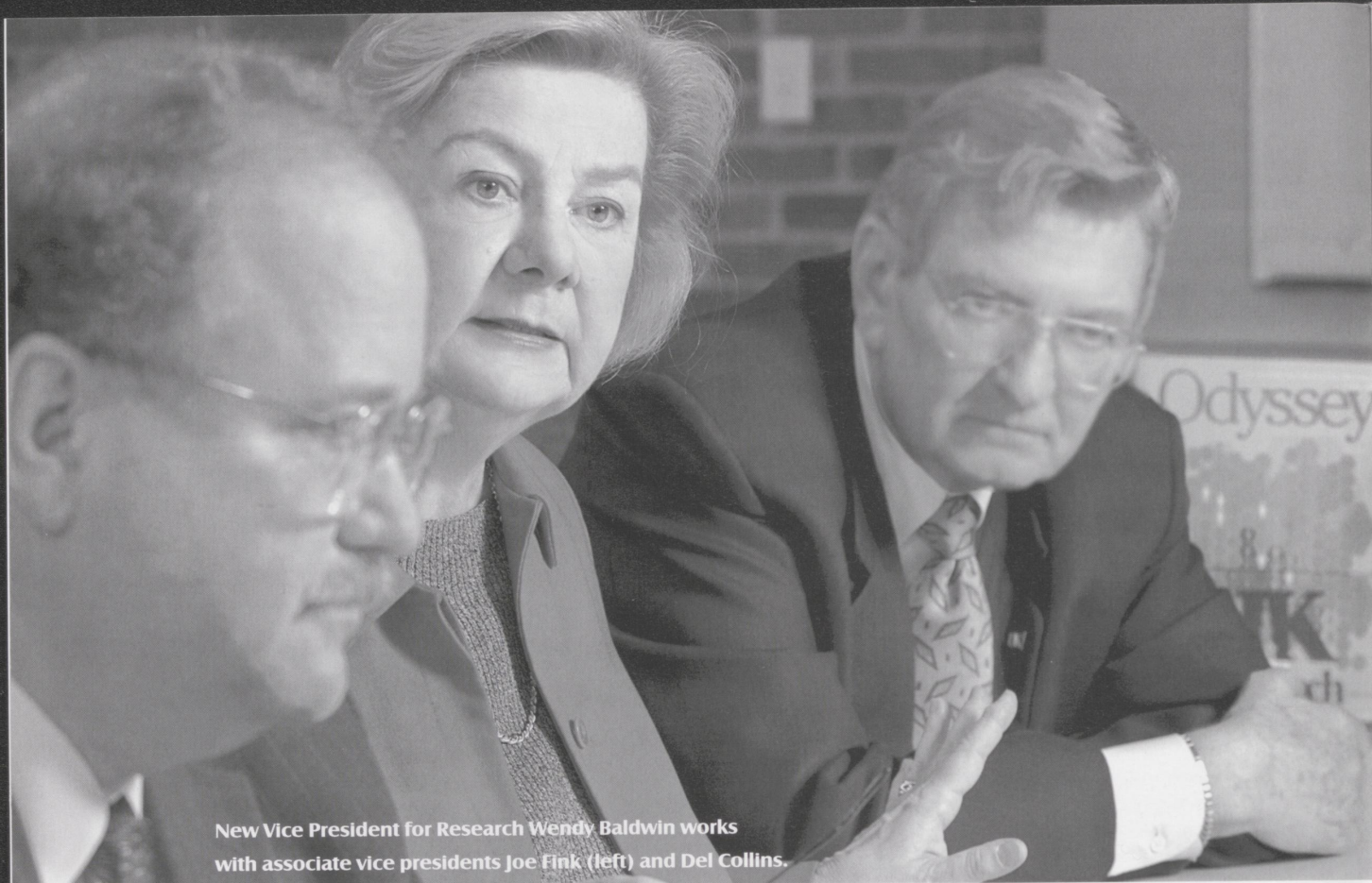


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New Vice President for Research Wendy Baldwin works with associate vice presidents Joe Fink (left) and Del Collins.

From the Beltway to the Bluegrass

WRITTEN BY
Jeff Worley

The University of Kentucky's new vice president for research feels like she's come home. "Yes, even though it's been 30 years since I left UK as a freshly minted Ph.D., I do feel like I am 'coming home,'" says Wendy Baldwin, who took over UK's more than \$200-million-a-year research enterprise the first of this year. After receiving a B.A. in sociology in 1967 from Stetson University in Deland, Florida, she worked in New York City as a social worker. But then a simple phone call changed her life.

"A good friend of mine working on a Ph.D. in sociology called me from Lexington. 'You ought to come here,' she said. 'They have a great sociology program.' So I decided to come to UK sight unseen. I squeezed all my possessions—and my two cats—into my Austin Healey 3000, and headed for the Bluegrass," says Baldwin, who had never been to Kentucky.

A Pennsylvania native, she earned two advanced sociology degrees from UK: a master's in 1970 and a Ph.D. in 1973.

Baldwin, whose affable and engaging nature strikes you immediately, brings to UK 30 years of experience at the National Institutes of Health (NIH) in Bethesda, Maryland, one of the nation's largest federal funding agencies, where for the past nine years she served as deputy director for extramural research. She says extramural research is the largest part

**“For some time now,
I’ve been holding
up Kentucky as an
example of how the
state/university
working relationship
can be mutually
beneficial.”**

—Wendy Baldwin

of NIH, accounting for over 80 percent of the \$27 billion annual budget. Each year the agency supplies funding to more than 50,000 investigators affiliated with 1,700 universities, small businesses, academic medical centers, and other research facilities worldwide through a process of competitive peer review.

Baldwin says there were two primary reasons she wanted to come to UK. “I think the university is poised to grow academically, and the administration is totally committed to strengthening UK. There is such energy here to build the research program, and it seemed like my background was a good fit with UK’s goals.”

Baldwin was also impressed with Kentucky’s commitment to higher education that resulted in the Research Challenge Trust Fund (RCTF), more commonly known as Bucks for Brains, which was established in 1997. (For more information on RCTF, go to www.rgs.uky.edu/ca/rctf.) “For some time now, I’ve been holding up Kentucky as an example of how the state/university working relationship can be mutually beneficial,” she says.

But Baldwin realizes she has arrived at UK at a challenging time. “Most states are facing hard choices in their budgets—Kentucky is not alone,” she says. “Despite this, we need to repeat our message over and over: when the state supports the mission of a research university—a crucial partnership—there are not only significant economic returns and intellectual returns, but also advances in the quality of life for our citizens.”

Building various types of partnerships has been Baldwin’s stock-in-trade at NIH. “I went there on a two-year appointment and, well, those two years

turned into 30.” She says she particularly enjoyed working on extramural funding with universities like UK. “NIH can’t fund research unless there are universities out there that can do the work. Most of my career has been spent working with the academic community to help them develop their research programs and also make successful applications to NIH.”

In her work at NIH, Baldwin has seen firsthand how extremely competitive research funding is, and she believes research universities can’t rest on their laurels when it comes to funding successes. She says one way research universities can stay competitive is to continually look at how they are supporting their researchers, especially new faculty. “It’s hard to get started in research, and it’s important that young talent be nurtured. That has implications for how postdocs are treated, how an office like mine is able to demystify the process of seeking external funding, and how seed money is made available,” says Baldwin.

Another challenge, she says, is the need to link up researchers who have common interests. “Universities and the federal funders are all struggling with how to identify those areas that truly need an interdisciplinary approach and then how to ensure that people can work together effectively. That goes to the heart of how an institution is organized: Does the system reward faculty who work together across

department or college lines?”

Baldwin, whose enthusiasm and energy are contagious, is looking forward to these challenges at UK while focusing on her primary goal of helping to build research programs. “One of the things I’m proudest of at NIH was helping to create a bioengineering consortium. The problem had been that bioengineering was spread all across the 24 NIH institutes and centers. We were able to bring all of that together and launch a new program that has put about \$150 million into this area for the NIH,” Baldwin explains.

Breakthroughs in bioengineering research, she says, can directly affect our health and well-being. In the biomedical arena, for example, the genome project has taken giant steps in mapping the genome; now the challenge is to understand how those genes function and the role of proteins. These advances will eventually help us better understand diseases and enable us to successfully target therapies.

Baldwin has also worked on a broad array of policy issues such as human subjects protections, reduction of regulatory burdens and conflicts of interest. “These are all issues that are critical for universities to address and that call for a strong partnership with the federal government,” she says.

“Right now, I’m doing a lot of listening,” Baldwin says. “I’m interested in what our faculty think about current research programs and about launching new programs. I also want to work with faculty and staff to further strengthen our outreach efforts. As Kentucky’s flagship university, we have a bottom-line responsibility to do what we can to improve the lives of Kentuckians.” ■

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

Clinical trials have suffered their share of tribulations lately.

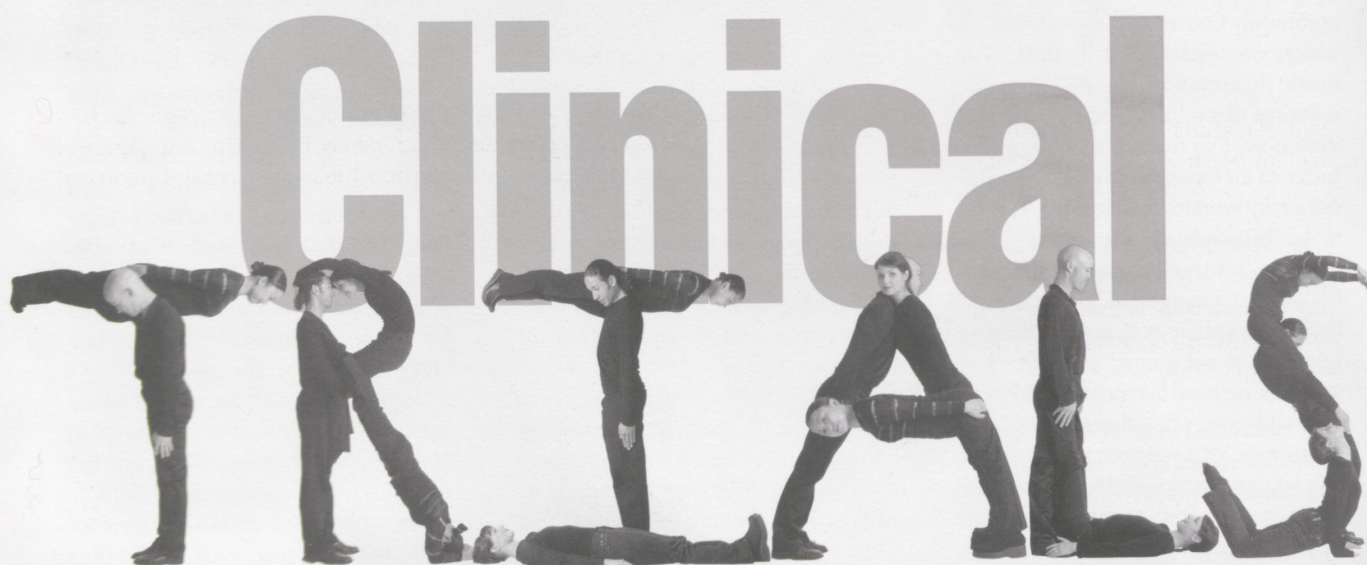
The April 22, 2002, issue of *Time* included a lengthy article titled "At Your Own Risk" that chronicled the slipshod study headed up by Dr. Michael McGee at the St. John Medical Center in Tulsa, Oklahoma. His experimental vaccine for malignant melanoma, a particularly nasty type of cancer, was making over a third of the trial's participants sick, a fact that McGee kept to himself before the trial was shut down.

Far more serious was the outcome of a clinical trial in Maryland. Ellen Roche, 24, a technician at the Johns Hopkins Asthma and Allergy Center, was one of three healthy volunteers who agreed to participate in a Hopkins clinical asthma trial to evaluate the effects of a chemical irritant. Two days after inhaling the chemical, Roche developed a cough, fever and muscle pain. These ailments soon led to respiratory distress, and within a month she was dead.

These incidents—and others that have been spotlighted in the press—have led some people to overgeneralize the dangers of clinical trials.

"Although there are some risks associated with most clinical trials, the truth is that clinical trials are usually very safe—the vast majority of subjects are not harmed," says Ada Sue Selwitz, director of the Office of Research Integrity (ORI) at the University of Kentucky. The ORI supports six federally mandated review committees: three Medical and a Nonmedical Institutional Review Board (IRB), the Institutional Animal Care and Use Committee, and the Radioactive Drug Research Committee.

"Clinical trials are a vital and necessary part of America's medical research system. They have proven to be the best mechanism for testing potential drugs and separating the ones that work from the ones that are ineffective or potentially harmful," says Selwitz, who is past president of the Applied



A Human Safety Net for New Drugs and Treatments

Research Ethics National Association and currently a member of the NIH Regulatory Burden Working Group. "Almost all medical and bioethical experts agree that it's important to have clinical trials and that it's equally essential to put into place protective safeguards for patients."

Assuring that these safeguards are in place is at the heart of IRBs. At UK, the IRB—a group of doctors, other health-care providers, and community members—reviews all research studies to protect the rights of research volunteers and ensure that the study doesn't cause unnecessary risk to participants. Selwitz says that even before it was required by federal regulations in 1981, UK established an institutional review board because the university "has always been committed to conducting ethically appropriate research."

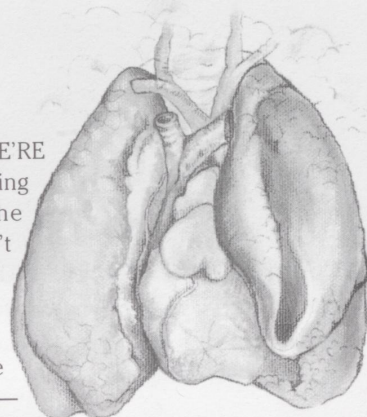
Across campus in his VA Hospital office, John Thompson, who has been a professor of medicine at UK since 1980, helps researchers with the nuts and bolts of clinical trials. Thompson now heads up the University of Kentucky Clinical Research Organization (UKCRO), which does everything from helping to train researchers on how to conduct clinical trials to providing the critical link between faculty and industry. [For more information on UKCRO, go to www.mc.uky.edu/ukcro.]

"The bottom line is, there is a web of protection that governs clinical research," says Wendy Baldwin, UK's new vice president for research. "The IRB is a vital part of this web, but we shouldn't lose sight of the importance of educating all our staff who are conducting clinical studies. Trained staff are really the front line in protecting people who participate in clinical trials. Other safeguards include data safety monitoring boards that are specifically constituted to assess ongoing risks and benefits of a trial and federal agencies such as NIH and the FDA, which provide additional oversight," says Baldwin, who brings 30 years' experience at NIH to her position at UK [see article on page 2].

There are currently 531 clinical trials under way at UK, according to Larry Iten, associate director of the ORI. Over 1,400 researchers are involved in these trials, and many work on more than one. For more information on how to participate and the research expertise available at UK, go to www.mc.uky.edu/research/clinicaltrials.htm. Meanwhile, read about six of these research trials in the pages that follow.

Lung cancer

The headlines blared WE'RE NUMBER 1! The news being trumpeted wasn't in the sports section. This wasn't about Kentucky basketball. It was about the latest lung-cancer rates in the United States, and the bad—but not surprising—news was that Kentucky's 1999 lung cancer numbers led the nation among men and women.



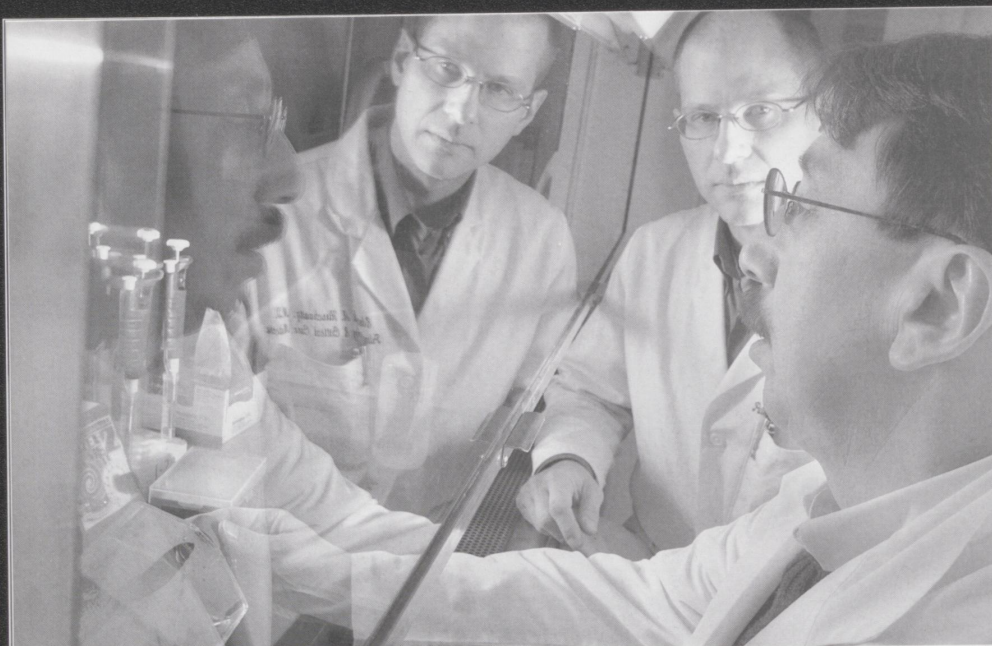
"Kentucky stands out not only as the number one state, but it's been that way for a long time," says Timothy Mullett, a lung surgeon and director of the University of Kentucky's Multidisciplinary Lung Cancer Program. This year it's estimated that 3,100 Kentuckians will die of lung cancer. "There's about 50 percent more lung cancer in Kentucky than the national average," says Alfred Cohen, director of UK's Markey Cancer Center. "That's catastrophic."

The disease kills 75 to 80 percent of those it infects. According to the American Cancer Society, this year more people will die from lung cancer than from breast, prostate and colorectal cancers combined.

Two UK researchers are working to reverse these stats with

"The beauty of this vaccine is that it stimulates cells to attack only tumor cells. It does not attack normal tissue as past treatments have. These cells that we create are very, very smart."

—John Yannelli



John Yannelli (foreground) and Edward Hirschowitz have created a novel vaccine to reduce the risk of lung cancer recurrence. Kentucky's 1999 lung cancer rates were the highest in the nation among men and women.

a novel vaccine they created to reduce the risk of lung cancer recurrence. John Yannelli, an associate professor of medicine, and Edward Hirschowitz, an assistant professor of medicine, are heading up a two-year clinical trial that will involve up to 30 patients diagnosed with non-small lung cancer who have already undergone surgery, radiation or chemotherapy. Non-small lung cancer is moderately fast-growing and best treated by surgical resection, and according to Hirschowitz, accounts for 75 percent of all diagnosed lung cancers. The trial is being funded by the Kentucky Lung Cancer Tobacco Settlement Fund and the Cancer Treatment Research Foundation, a national philanthropic agency based in Chicago.

"Although the vaccine will not prevent lung cancer in those who have never had it, we're hoping that it can prevent the disease from returning and help maintain remission periods after treatment," Hirschowitz says, as reported in the *Lexington Herald-Leader* last June, adding that even after lung cancer surgery that is deemed "successful," patients have a 15 to 50 percent chance of recurrence. "Because additional medical therapies are not generally recommended until recurrences are seen, we are using the window between medical and surgical therapy and recurrence to enhance the body's immune response to residual cancer."

Hirschowitz and Yannelli, with the aid of what Yannelli calls a "very talented and indispensable" support staff, make this vaccine in an eight-step process. First, through a procedure called leukapheresis, the patient's dendritic cells—the most potent immune-inducing cells in the body—are taken. Technicians duplicate them in the lab and mix them with cancer

proteins derived from lung cancer cells. Once the dendritic cells ingest the lung cancer proteins, they are retrained to direct the immune system to target and kill cancer cells.

"This process takes seven days," Yannelli explains. "We've grown the number of cells up to very large numbers: at seven days we harvest a hundred million dendritic cells." The researchers put the cells, which are now in full combat gear, in an injectable saline solution, the vaccine.

"The beauty of this vaccine," Yannelli says, "is that it stimulates cells to attack only tumor cells. It does not attack normal tissue as past treatments have. These cells that we create are very, very smart."

Each patient receives two three-milliliter injections of the dendritic cells, one month apart. The researchers think that when the cells are delivered to the patient, they will travel to the lymph nodes and stimulate the immune system to seek and destroy cancer cells. "We don't know everything about the immune system, but we're taking advantage of what we do understand, letting the biology take care of business in reacting to an infection or other foreign proteins," Hirschowitz says.

There have been no major side effects from the injection so far in the trial, Yannelli says, only local reactions such as a small welt similar to what any of us might see after an allergy shot.

"We're doing something during a time when nothing else is offered," Hirschowitz says. "You can either sit on the couch waiting for your cancer to grow, or you can try something."

"Lung cancer is particularly aggressive," adds Yannelli. "We expect a recurrence—if there is one—to happen within three years. If someone doesn't have a recurrence in five years, they're cured. My fondest hope is to see my patients back in the clinic in five years and say—as they leave the room—'See you at the UK game.'"

For information on how to participate in this clinical trial, call the Pulmonary Research Office at 859/257-9575.

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M

acular Degeneration

"The eye is an extremely unforgiving organ," says Jayakrishna Ambati, an associate professor of ophthalmology at UK. "And because of this, our work is all the more challenging."

The eye places a premium on optical clarity, he explains, and new blood vessels that grow in the eye interfere with clarity and are the main culprits in driving the disease called macular degeneration.

Why do new blood vessels grow? "The truth is, we aren't sure," says Ambati. "It could be because as the eye grows (it's about 50 percent larger when we're adults), various deposits form in the back of the eye and promote a mild degree of inflammation, which may trigger the formation of new blood vessels." As new blood vessels develop, they bleed and leak fluid because they're so fragile, and injure the retina.

"Unfortunately, all this is happening in the tiny, one-millimeter region in the center of your eye. If it happened anywhere else, it wouldn't be much of a problem."

Ambati, working with UK ophthalmologist Andrew Pearson, is trying to find answers to basic biological questions about diseases of the eye, specifically—in two ongoing clinical trials—the origin and progression of age-related macular degeneration (AMD).

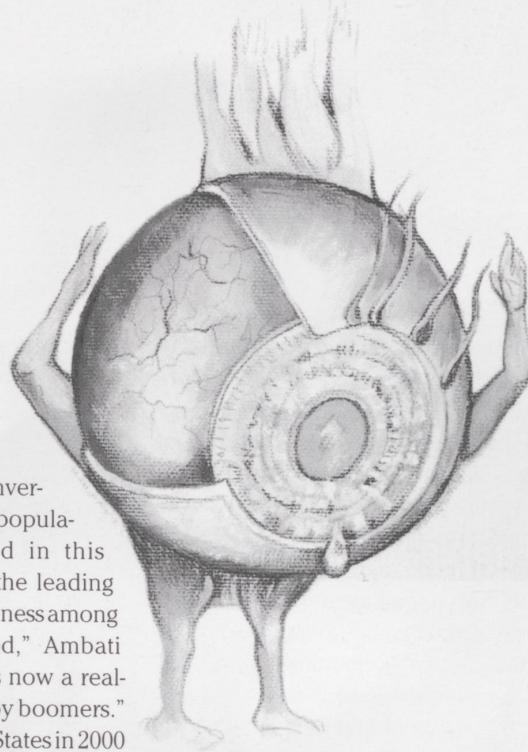
"AMD is the leading cause of blindness not only among the elderly in this and other developed nations, but be-

cause of the inversion of the population pyramid in this country, it's the leading cause of blindness among adults, period," Ambati explains. "It's now a reality for the baby boomers." In the United States in 2000 there were 35 million senior citizens (12.4 percent of the population was over the age of 65), according to David Wekstein, associate director of UK's Sanders-Brown Center on Aging. This number is expected to grow to around 40 million by 2010 and to 70 million by 2030.

"We are clearly becoming a more geriatric population," says Ambati, "and therefore diseases associated with aging are of tremendous public health importance."

Currently, the only approved treatment for AMD is something called photodynamic therapy (PDT), which involves injection of the dye visudine. This drug accumulates preferentially throughout the body, but not solely, in areas of new blood vessels. "We use a laser beam to activate that drug, which then closes off blood vessels and causes them to stop leaking," Ambati explains. But this treatment, he adds, "leaves a lot to be desired."

For one thing, only about 20 percent of people with macular degeneration are eligible for this treatment—those who fall into the category of "classic



Once approved, a clinical trial goes through four phases:

Phase I: Researchers give the drug to a small number of people to see what dose is safe.

Phase II: Researchers give 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.

Phase III: Researchers give the drug to a much larger group of people over several months or years to see whether the drug remains useful or has any side effects that only show up after a longer period of time.

Phase IV: Researchers continue to study the drug even after it has been approved in what are called "post-marketing" trials. They can then watch for any side effects or problems that may show up after several years of treatment.

leakage." "Most patients have the other type, occult leakage, which doesn't respond well at all to photodynamic therapy." Ambati is quick to add that PDT doesn't restore vision; all it does is decrease the rate of vision loss. "Also, it's not a permanent effect—95 percent of these vessels re-open within two to three months, so treatment has to be repeated over and over again."

In one of their current clinical trials—a Phase II trial focused on patients with occult age-related macular degeneration—Ambati and Pearson are testing the effectiveness of an implant containing the steroid fluocinolone acetonide. Steroids have long been known to be potent anti-inflammatory agents, and the idea in this study is to deliver high doses to the eye and no place else, since steroids given systemically are known to have severe side effects. The

"Next to life itself, vision is the most precious thing we have. When people get older and enter their retirement years, they have more time to read and to watch television, and obviously they want to continue to be able to see the faces of their grandchildren. Macular degeneration robs them of all these things."

—Jayakrishna Ambati

doctors will target the eye by implanting a device called Envision TD, developed in part by Pearson at the UK Chandler Medical Center. The device is a tiny polymer shell containing about two milligrams of the drug.

The trial, which is scheduled to run until March 2006, is fully enrolled and is well under way, with 50 trial participants placed at random into three groups: one gets a placebo, one gets an implant, and the third gets the implant and photodynamic therapy. (Ambati did the implant procedure for those who fell into groups two and three. While the patients were awake and under local anesthetic, he inserted the device during a 15-minute procedure, suturing the polymer shell in place.)

Though he's clearly excited by the basic science of trying to better understand the causes of macular degeneration, Ambati prefers to talk about how such work can help people.

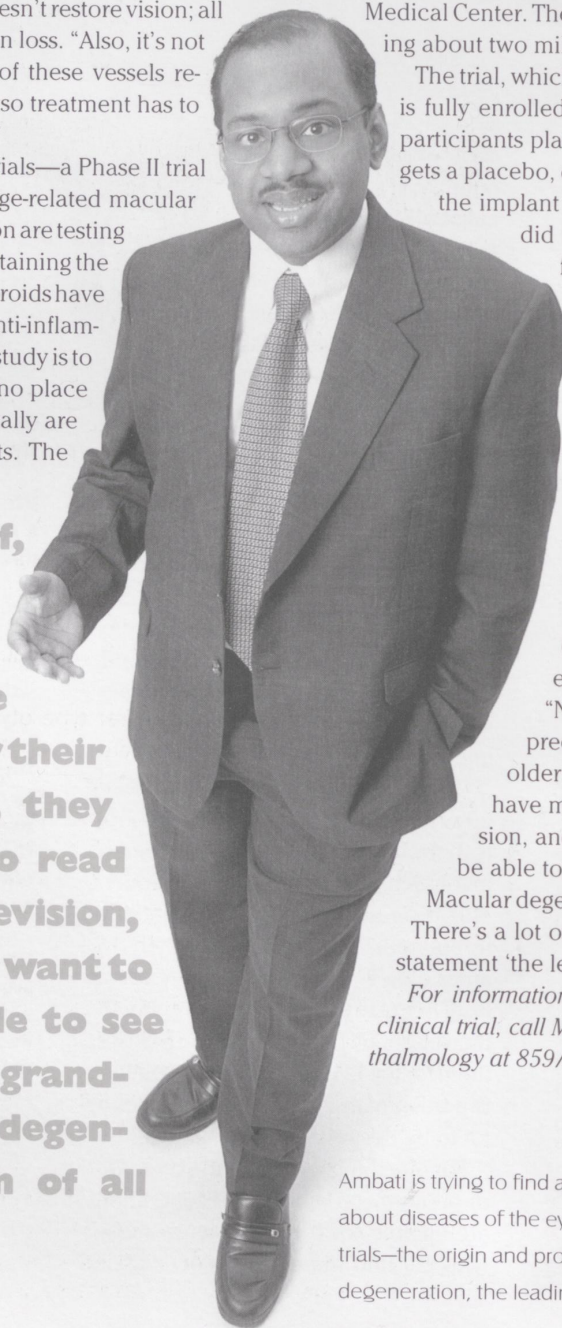
"Around 25 percent of people over 65 have some form of macular degeneration—that's a huge number," he says.

"Next to life itself, vision is the most precious thing we have. When people get older and enter their retirement years, they have more time to read and to watch television, and obviously they want to continue to be able to see the faces of their grandchildren.

Macular degeneration robs them of all these things. There's a lot of human suffering behind the simple statement 'the leading cause of blindness.'"

For information on how to participate in a related clinical trial, call Michele Reg in the Department of Ophthalmology at 859/323-5868.

Ambati is trying to find answers to basic biological questions about diseases of the eye, specifically—in two ongoing clinical trials—the origin and progression of age-related macular degeneration, the leading cause of blindness in adults.



D

iabetes

pancreas

"We have an epidemic of diabetes in this country, and unless there's a lot more attention paid to this disease, the problem is just going to get worse."

This pronouncement comes from Dennis Karounos, an associate professor in the Division of Endocrinology and Molecular Medicine at UK and the VA Medical Center, who says that the risk is increasing for people with both of the traditional forms of diabetes—type 1 and type 2. Type 1 diabetes, previously called insulin-dependent diabetes mellitus or juvenile-onset diabetes, may account for 5 to 10 percent of all diagnosed cases of diabetes. Type 2 diabetes, previously called non-insulin-dependent diabetes mellitus or adult-onset diabetes, is estimated to account for about 90 to 95 percent of all diagnosed cases.

Karounos explains "previously."

"It used to be we'd hardly ever see a child with type 2 diabetes; now 30 percent of children who have diabetes have type 2, an alarmingly high number."

In 2001, 16.7 million Americans were diagnosed with diabetes, according to a study by the Centers for Disease Control and Prevention published in the *Journal of the American Medical Association* last December. In Kentucky in 2001, 6.6 percent of people had been diagnosed with diabetes, a steady percentage climb since 1994.

One reason for this increase, Karounos says, is simple demographics. "Baby boomers are headed right



Dennis Karounos is testing a vaccine to treat latent autoimmune diabetes, a common but unfamiliar type of adult-onset diabetes. In 2001, 6.6 percent of Kentuckians were diagnosed with diabetes, a steady percentage climb since 1994.

for their 60s and 70s, when people become more prone to developing diabetes because, when we're older, the pancreas produces less insulin," he says.

Karounos came from Baylor University 12 years ago and is director of the diabetes program at UK. He is currently focusing his work on what might be called a hybrid type of diabetes—type 1½, which is also called latent autoimmune diabetes in adults (LADA).

"This is a common but unfamiliar type of adult-onset diabetes," he explains. "LADA is a disease like type 1 diabetes in which the body's immune system attacks and destroys insulin-producing cells in the pancreas, decreasing the body's ability to produce insulin."

In testing a vaccine to treat LADA, Karounos is working with James Anderson, a professor in the UK endocrinology and molecular medicine division who has been researching diabetes for nearly 30 years. In this Phase II clinical trial, they are teaming up with researchers at Washington University in St. Louis, and the universities of Colorado, Alabama, and Washington in Seattle.

"In order to tackle the problem of type 1½ diabetes clinically, we started looking around at different therapies that are out there," Karounos says. "Lo and behold, there was a group in Israel using an experimental drug that clearly improved insulin secretion in people who'd just developed type 1 diabetes."

For this UK trial, Karounos initially screened, through a blood sample, potential patients recently diagnosed with type 2 diabetes. He looked for antibodies that indicate the autoimmune form of the disease, and if these antibodies were present, and if the volunteers meet a couple of other criteria, they were invited to join the trial.

The study is "double blind," which means neither the participant nor the physician knows whether the experimental drug is being administered. The 20

participants will get eight injections over two years. Half will get the vaccine; half will get an inactive shot.

As reported in the *Lexington Herald-Leader* last November, Angela Blythe, a UK pediatric nurse, was one of the first two people enrolled in the UK study. Her blood test found she has the autoimmune form of the disease.

"I hope I never have to get to the point of needing insulin injections," she says. "The trial is a chance to test something that could get rid of this so that I never have to worry about it." About 80 percent of people who have Blythe's type of diabetes eventually need daily insulin shots, Karounos says.

The vaccine has exciting potential, he says. If found to halt the progression of diabetes by protecting the insulin-producing cells of the pancreas, the vaccine could be injected every three to six months—"something like a targeted allergy shot for pancreatic cells," Karounos says.

If successful, the vaccine could eliminate or decrease the need for insulin injections for up to 25 percent of people with adult-onset diabetes—up to 3.2 million Americans.

"We're hoping to prevent people from becoming dependent upon insulin therapy," Karounos says. "Diabetes typically affects a person's quality of life. Right now, there's no cure for diabetes, but with new drugs we will be better able to control it."

For information on how to participate in this clinical trial, call UK's Metabolic Research Group at 859/257-4058.

Protecting Human Subjects in Research

"There are a lot of players who share responsibility for the protection of human subjects in research," says Ada Sue Selwitz, who has shaped UK's research oversight activities since 1979.

It all begins with the researcher who is required by federal law to bring his or her project before the appropriate institutional review board (UK has three IRBs for medical research and one for non-medical projects). The IRB, a committee of health-care professionals and community members, reviews the protocol to look at the ethics of the research before deciding whether or not a trial can begin. After the research protocol is approved, there are several points at which the IRB continues to review the project: periodic review for continuing projects, review when there is any modification to the protocol, and reviews when any unanticipated problems or adverse effects are reported.

Selwitz points to the peer review system for federally funded research as another protection for clinical trial volunteers. "Even before a project is funded, other scientists may be raising ethical concerns about a proposal," says Selwitz.

During the life of a clinical-trial project, the researcher is required to provide periodic reports to the sponsor. The sponsor, in turn, is required to report any problems to the FDA.

In a large clinical trial, another safeguard is the Data Safety Monitoring Board, comprised of scientists who monitor a trial's progress and who have the authority to stop a trial if they have concerns about data as it comes in. If a trial does not have a monitoring board, a researcher is required to set up a data safety monitoring plan.

The Office of Human Research Protections, a federal IRB regulatory agency in the Department of Health and Human Services, has the responsibility to ensure that an institution conducting clinical trials is in compliance with federal regulations and policies for the protection of human subjects in research.

The University of Kentucky will expand its mandatory human subjects protection training program this fall to include all key personnel on projects involving human subjects. Over 900 UK researchers have already completed this required education program.

Hormone Replacement Therapy

To be or not to be on hormone replacement therapy (HRT)—the use of prescription drugs to “replace” the hormones estrogen and progesterone that the ovaries quit making at the time of menopause—is a major question many postmenopausal women are trying to answer.

It's a difficult question because of some findings from the NIH's Women's Health Initiative (WHI) that were released last July. The NIH halted its trial of combination hormone replacement therapy (estrogen and progestin)—citing long-term risk factors such as increased risks for heart attack, stroke and breast cancer. And for millions of women the news, as aptly put in a *Time* article, “struck like a hot flash.”

The report concluded that for some women, the risks HRT outweigh the benefits (less osteoporosis and lower colon-cancer rates). And the HRT choice isn't made any easier by the fact that, right now, it's the only medical therapy available to provide relief from acute symptoms of menopause, such as hot flashes and night sweats.

To make matters worse, shoddy reporting has fueled public confusion. For example, a wire-service story that made the rounds last January cited the Food and Drug Administration as saying, “women should not take estrogen or combinations of estrogen and progesterone.” The previous day's FDA news release, however, said no such thing. The release focused instead on new FDA guidance for manufacturers

of estrogen and estrogen with progestin products regarding the language that should be used on the product label.

“Before the WHI results were announced, it was thought that HRT use would cut heart attack risks in half,” says Ken Muse, associate professor of obstetrics and gynecology in the UK College of Medicine. “A major finding in the study was that with HRT, even though there's an improvement in cholesterol results, the risk of heart attack and stroke increases.”

Muse says that because of these findings and the subsequent new and important questions about the benefits and risks of HRT, this is a particularly exciting time to be doing research in this area. “It's a tremendous clinical question right now—both in the woman's mind and doctor's mind: How do you treat menopausal women? What's the best way to balance the benefits and risks?”

In September of 2000, Muse and a group of behavioral investigators at UK including Thomas Kelly, professor of behavioral science, initiated a clinical trial to evaluate the effects of raloxifene on behavior, memory and mood, a focus that has gotten scant attention, and was not part of the NIH study. Raloxifene is the first of the “designer estrogen” medicines, which have some of the effects of estrogen, but few, if any, of the drawbacks.

The trial is being conducted as part of the \$8.3 million Center for Biomed-

“Physicians are convinced that quality-of-life benefits that result from taking Hormone Replacement Therapy, such as suppression of hot flashes and improved sleep, are important. There hasn't been much work done, though, on how HRT affects such things as mood, memory and clear-headedness, so we need to find out if there are benefits here as well.”

—Ken Muse



Thomas Kelly (left) and Ken Muse are evaluating the effects of raloxifene, the first of the "designer estrogen" medicines, on behavior, memory and mood. The clinical trial is being conducted as part of the \$8.3 million Center for Biomedical Research Excellence in Women's Health, funded by NIH. This is the single largest grant ever awarded in the area of women's health at UK.



cal Research Excellence (COBRE) in Women's Health, funded by the NIH. This is the single largest grant ever awarded in the area of women's health at UK.

"The COBRE study is particularly crucial because most patients and most physicians are convinced that quality-of-life benefits that result from taking HRT, such as suppression of hot flashes and improved sleep, are important," Muse says. "There hasn't been much work done, though, on how HRT affects such things as mood, memory and clear-headedness, so we need to find out if there are benefits here as well."

In this study postmenopausal women who are not taking any form of HRT are evaluated for memory, object orienta-

tion and mood through a battery of tests, including brief computerized tasks and questionnaires as well as the evaluation of urine and blood samples. The women are then given estrogen, raloxifene (which targets only specific parts of the body), or a placebo.

Hormone effects will be determined by comparing behavioral measures before therapy began with those taken after one and six months of daily treatment. Kelly says the original plan was to do a one-year trial, but because of the recent NIH data on risks from long-term use, he and Muse cut the length of the study in half.

"Everybody agrees we need more research on HRT," says Vivian Pinn, head of the NIH's Office of Research on Women's Health, who was quoted in

Newsweek. "It's taking time, but more answers are coming."

"Many central Kentucky women are taking an active role in helping solve these problems by participating in this research," Muse says. "We're happy to have this opportunity at UK to be leaders in advancing the science of women's health medicine."

For information on how to participate in this study, call 859/277-3799.



Patricia Burkhardt in the College of Nursing holds an electronic peak-flow monitor, which records data about a child's breathing rates. She is heading up a clinical trial to evaluate different ways of teaching kids with persistent asthma to self-manage their condition at home.

Asthma

It takes many researchers some time—years maybe—to find their niche. In Pat Burkhardt's case, her research focus found her.

"Twenty-four years ago my son, Kevin, was diagnosed with asthma when he was two years old," says Burkhardt, an assistant professor in UK's College of Nursing. She began to read everything she could about childhood asthma. This intensive study led her to a Ph.D. in nursing with a research focus on child asthma and to recently being certified as an asthma educator by the American Lung Association.

According to the Centers for Disease Control and Prevention, asthma is the most prevalent chronic condition among children in the United States, affecting over eight million children, including 70,000 in Kentucky. And here's an even scarier statistic: while death rates for many diseases are falling, the mortality rates for children age 19 and younger with asthma increased by 78 percent between 1980 and 1993.

Burkhardt says that while there's wide agreement on the genetic predisposition for asthma, it's tough to definitively pin down other causes.

"Some epidemiologists say that children are experiencing heavy-duty allergens because our houses are so airtight. Then there's the older theory about keeping your kids from close contact with other kids, such as in day-care centers, because they'll pick up more colds and develop airway inflammation that can lead to asthma."

The problem is, she says, these theories have tended to change over the years. "Here's another theory: since we've used antibiotics extensively, maybe childrens' immune systems aren't strong enough to combat bacteria and viruses." She adds that having pets in the household also used to be taboo, but now some clinicians think kids who are exposed to animals early tend not to be allergic to them later in life because, through such contact, children build up the necessary antibodies.

Despite the confusion about what causes asthma, Burkhardt says that blame for increased rates in morbidity and mortality among children with the disease may be a

lack of early intervention, lack of knowledge regarding self-management, and non-adherence to prescribed treatment regimes. In a clinical trial funded by the National Institute of Nursing Research at NIH, Burkhart is working to help resolve these issues.

Her two-year trial will involve 86 children ages 7 to 11 with persistent asthma. As principal investigator, she will evaluate different ways of teaching kids to manage their asthma at home using a device that electronically gathers data.

What Burkhart hopes to achieve through an educational and behavioral intervention is to increase children's adherence to daily peak expiratory flow rate (PEFR) monitoring. Peak-flow monitoring is integral to asthma self-management for patients with persistent asthma in order to assess the existence and severity of airflow obstruction. However, there are no published studies on how to promote children's adherence to daily self-monitoring.

"Peak-flow meters are simple, handheld monitors," Burkhart explains, "that can detect airway obstruction, often before any appearance of clinical signs." If a child blows into it and the number falls during the day, this indicates that the airways are starting

to constrict, even before coughing, wheezing or shortness of breath occur. The child can then intervene early to prevent a major asthmatic episode. During the trial, each child will use an electronic peak-flow meter that records the date, time and peak-flow value. It also includes a self-report symptom and medication diary.

Burkhart was the first nurse researcher to use a microprocessor-based peak-flow measurement instrument. "This is the centerpiece for this clinical trial and a huge advance over the less accurate self-report asthma diaries that have been traditionally used. Now, objective data can be downloaded to a computer and gathered electronically," she says.

In this study the intervention group will receive intense asthma education. The control group will get the usual care, she says. "Typically, the health-care provider will simply say, 'Here's your peak-flow meter. We'd like you to blow into it every day. Record your numbers in a diary and send it in to us,'" Burkhart says, adding that adherence issues regarding regular peak-flow monitoring are generally not addressed.

The intervention group (children and their parents) will have five one-on-one sessions with a pediatric nurse, while the control group will have three one-on-one sessions during a 16-week period. Both groups will be asked to perform daily peak-flow monitoring at home and to record their peak-flow values, asthma symptoms, and medications in an asthma diary.

"The first thing we do with the intervention group is to teach kids what

**"With the
microprocessor-based
peak-flow instrument,
objective data
can be downloaded
to a computer."**

—Pat Burkhart

their peak-flow numbers mean," Burkhart says. "We have them blow into the meter in the morning and in the evening for two to three weeks so we can determine their 'personal best'—their highest number—to get a baseline. Then we determine their 'zones,' which are color-coded, based on their personal best value." She teaches children to think of their zones in terms of a traffic light.

An action plan is put in place so that the child and parent know exactly what to do for each zone. "Green means your asthma is under control. Yellow means take action. It indicates the child may need to add a bronchodilator medication and to increase the amount of inhaled corticosteroids in order to control the symptoms. If the peak-flow values drop into the red zone, we teach the children that they should head to the nearest emergency department."

Burkhart's own son, she says, has diligently used the meter and worked hard all his life to manage his asthma well and prevent asthma attacks. "He's 26 now and living in New York City," she says. "He's doing great—he recently ran in the marathon there and crossed the finish line with his family cheering him on."

For information on how your child can participate in the Children with Asthma Study, call 859/323-6874.



Thyroid Cancer

In his effort to better treat thyroid cancers, UK researcher Kenneth Ain is enlisting the aid of a drug with a universally despised reputation: thalidomide.

Thalidomide was introduced in 1957 in West Germany and was soon commonly prescribed to pregnant women as a sedative. When the drug was taken during the first trimester, however, it prevented normal growth of the fetus, resulting in horrific birth defects such as missing or shortened limbs in thousands of children around the world. These children, born in the late '50s and early '60s, became known as "thalidomide babies."

Ain, a professor of medicine in the Division of Endocrinology & Molecular Medicine at UK, believes that although thalidomide has been used inappropriately, that doesn't make it a "bad" drug. He points out that thalidomide has been FDA-approved to treat leprosy, for example, and Ain thinks the drug can help people with particularly hard-to-treat thyroid cancers.

"There has been some compelling anecdotal evidence that thalidomide given to a patient with anaplastic thyroid cancer, the most aggressive type of thyroid cancer known to man, retarded the growth of tumors for up to six months," says Ain, who came to UK in 1991 after spending four years at the National Institutes of Health. "So we wanted to do this current trial to test that out." Anaplastic thyroid cancer is rare—only 300 cases in this country each year—but it's deadly: from the time of diagnosis, even with therapy, patients typically live only four to five

months.

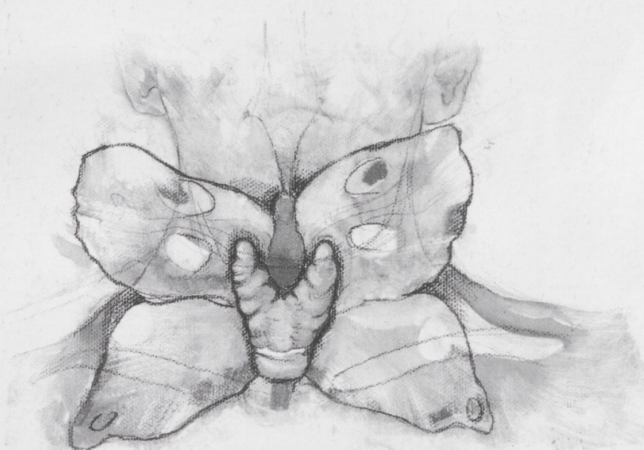
The thyroid gland is situated in the front part of the neck below the skin and muscle layers. This gland is shaped like a butterfly, with the two wings being represented by the left and right thyroid lobes that wrap around the trachea. The function of the thyroid is to regulate the body's metabolism. Thyroid cancer affects the gland responsible for producing hormones that control heart rate, body temperature and energy. It is diagnosed in nearly 15,000 women and around 4,500 men in the United States each year.

Over the past eight years, the incidence of thyroid cancer is on the increase for reasons, Ain says, that are unclear. He adds that fighting thyroid cancer is an especially tough challenge because no chemotherapy has been found to be effective.

Thyroid cells naturally pump in iodine to make the thyroid hormone, and thyroid cancer cells often retain this ability. This fact prompted investigators more than a half century ago to treat thyroid cancer, after the removal of thyroid gland, with radioactive iodine. "Time has demonstrated the effectiveness of this approach in most patients," says Ain. "Unfortunately, a subset of patients has rapidly progressive disease that does not respond to this treatment. For these patients, there haven't been any effective therapies."

But for such patients, desperation may soon be replaced by hope.

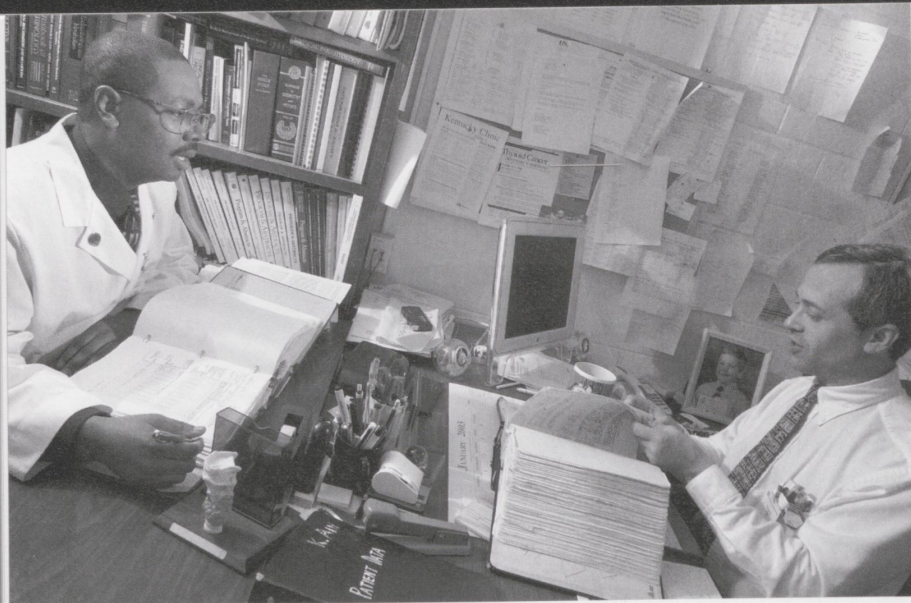
In a recent Phase II trial using thali-



domide to treat two types of thyroid cancers unresponsive to radioiodine, Ain and his team worked with patients who had rapidly progressive thyroid cancer. The participants were given up to 800 milligrams of thalidomide daily and were evaluated by CT scans every two months for a year; treatment was continued after each assessment if there was evidence that the cancer had stopped growing or had regressed. If the patient's tumor continued to grow as rapidly as before treatment, the patient was taken off this drug.

Of the 17 patients who have been evaluated, 13 experienced either a plateau or a decline in tumor size, and beneficial responses to thalidomide persisted for an average of seven months in half of these patients. In addition, patients who had experienced either a plateau or decline in their tumor size but eventually noted progression of their tumors lived longer than patients who had no beneficial response from the thalidomide—approximately four and a half months longer.

"These results suggest that thalidomide is a potent inhibitor of tumor progression in some aggressive, metastatic thyroid cancers," Ain says. "And patients with these advanced cancers badly need effective treatments because there are currently none available." Ain presented these findings at



Kevin Williams (left), a clinical research associate, and Kenneth Ain, a professor of medicine in the Division of Endocrinology & Molecular Medicine, discuss the latest results of a clinical trial using thalidomide to help people with particularly hard-to-treat thyroid cancers. Ain is heading up this study.

the Chemotherapy Foundation meeting in New York last December.

Funding for this trial came from the National Cancer Institute and the Celgene Corporation, a New Jersey-based pharmaceutical company. Further support came from UK's General Clinical Research Center, where much of this work took place. The center, located in the UK hospital, includes an outpatient clinic and a specimen-processing lab.

Ain emphasizes that the thalidomide trial is only one of several approaches under investigation at UK focused on understanding and treating thyroid cancer. This work is part of the well-established thyroid cancer program he began when he arrived at UK. The University of Kentucky Thyroid Nodule and Oncology Clinical Service is one of only a few such programs in the United States.

Ain reaches down to the floor and wrestles up a black book that is nearly two-feet thick. "These are my patients," he says, leafing through. "Right now I have hundreds of patients, and I follow every one of them." He adds that he

has one of the largest thyroid cancer practices in the world for a single doctor.

How can he work on several research projects, do the academic work required of him as a professor, and follow all these patients all at the same time?

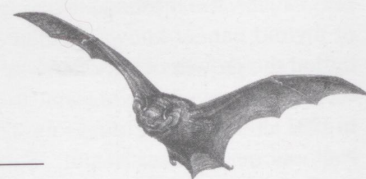
"It's an all-consuming job, I admit it. I work every day from 7:30 a.m. until anywhere from 11 at night to one in the morning. On weekends I catch up on my sleep—maybe six hours a night." And if Ain continues to spend long hours in the office, his wife-to-be, he says, will understand.

"Sara [Rosenthal] is a thyroid cancer survivor herself and a medical writer—she's written 35 books." When she wrote a book on thyroid cancer, she asked Ain to edit it for accuracy. "In the process I met her and fell in love." Rosenthal, whose expertise is in bioethics, will join the UK faculty this summer.

For information on how to participate in UK clinical thyroid cancer trials, have your physician call 859/323-3778. ■

"The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the decision."

—from the Nuremberg Code, "Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law," 1946-1949



What's the connection between bat saliva and stroke survival? In the Fall 2003 *Odyssey*, we'll tell you the story of a UK researcher who's testing what may become the most novel clot-buster ever—a new drug made from genetically engineered bat saliva.

WRITTEN BY
Debra Gibson

A Mouthful of Evidence

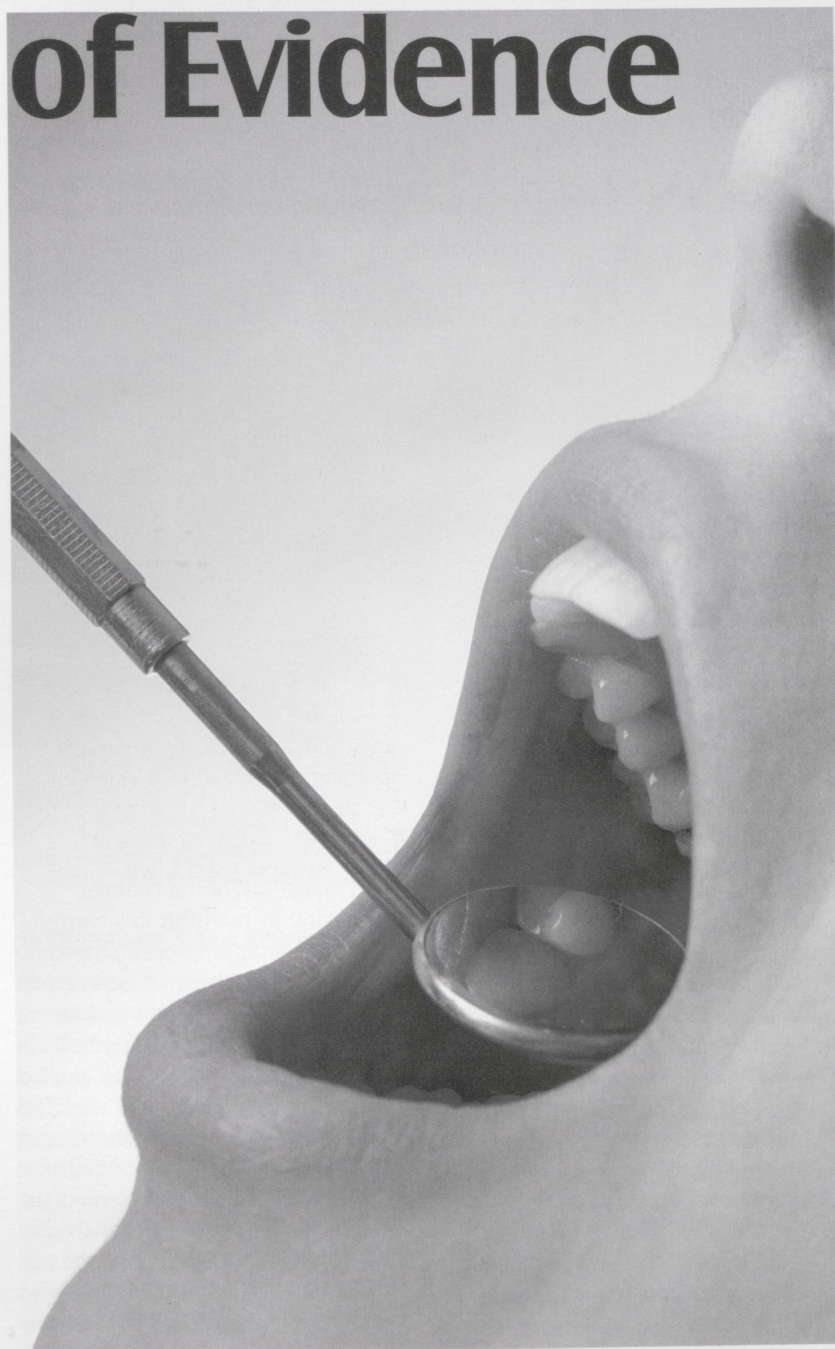
What's the link between periodontal disease and low-weight babies?

Pre-term and low-weight babies enter a different world from normal newborns. "Preemies" begin their lives in a world populated with incubators to keep them warm, ventilators to help them breathe. Often, the infants are subjected to phototherapy, a special light that bathes their body to metabolize a reddish-yellow pigment that can cause jaundice.

The vessels of preemies are so fragile that brain-bleeding is possible, and infection is a constant risk. These are only some of the dangers. And working to avert them has a price tag: when a premature baby is admitted to a neonatal intensive care unit, it costs an average of \$30,000 more than if the baby were healthy.

Nationally, an average of 12 percent of births are pre-term, and 8 percent of infants born have a low birth weight. In Kentucky, more than 4,000 infants are premature each year. Prematurity—which has increased by 27 percent in the United States since 1981—is the leading cause of death in this country within the first month of life.

Why some women cannot carry to full-term is not always clear.





Trying to Connect Cause and Effect

Doctors will tell you that the cause of low-weight births may be biological, chemical, genetic, or a combination of factors. At the University of Kentucky, researcher Jeffrey Ebersole, associate dean for research in the College of Dentistry, believes there may be another cause: periodontal disease.

In previous studies, researchers found that expectant mothers with periodontal disease may have a three- to seven-times greater risk of giving birth to premature and low-weight babies, and these findings made Ebersole want to investigate this possible link.

While important, findings from these studies are only "associational," he says, and do not prove cause and effect. "There are little data distinguishing whether the two problems are linked by causation or due to the same underlying risk factors," says Ebersole, who

also serves as director of UK's Center for Oral Health Research. Now, backed by a five-year, \$3.3 million grant from the National Institutes of Health, he is working to find a link between periodontal disease and low-weight babies. "Our goal is simple: we want to help make it possible for mothers to give birth to healthy, normal babies."

In trying to establish this cause/effect connection, Ebersole first needs to understand the cause of periodontal disease, an inflammatory condition of the gums and bone supporting the teeth that can ultimately lead to an erosion of the gums and the loss of teeth. So he's starting with bacteria that live in the mouth.

As far as bacteria are concerned, the mouth, home for more than 400 types of bacteria, is the perfect host. Some of these bacterial guests are good guys that live in the mouth symbiotically

and play a part in defending the body against infection by harmful bacteria. Other bacteria could kill us and—if they found their way via the bloodstream superhighway to other parts of the body, such as the brain, liver and heart—they would.

Under certain circumstances, the harmful bacteria may cause periodontal disease. But precisely which factors trigger bacteria to cause this disease is still a scientific mystery, Ebersole says.

"For decades, there appeared to be an easy answer: If you didn't brush your teeth, you'd get periodontal disease. But we now know that this answer is generally wrong," he says.

"There's no doubt that if you brush your teeth and floss, you will improve the health of your gums. But there is clearly a portion of the population that has very poor oral hygiene and yet does not get periodontal disease. There is also evidence that some people can take very good care of their teeth—brushing and flossing—and still get this disease. So it's not just a matter of the amount of bacteria in the mouth."

In trying to solve the mystery of periodontal disease, scientists become detectives. First, they identify potential suspects—individual bacteria—and examine them to determine their possible relationship with the disease. In this work researchers aren't starting from scratch. By now, the usual suspects in periodontal disease have been implicated in an array of medical problems.

Secondly, scientists are looking at known accomplices such as inflammation and genetics. The researchers hope these investigations will help them

discover what causes periodontal disease, an important step to prove the further cause and effect between the disease and the incidence of pre-term and low-birthweight infants.

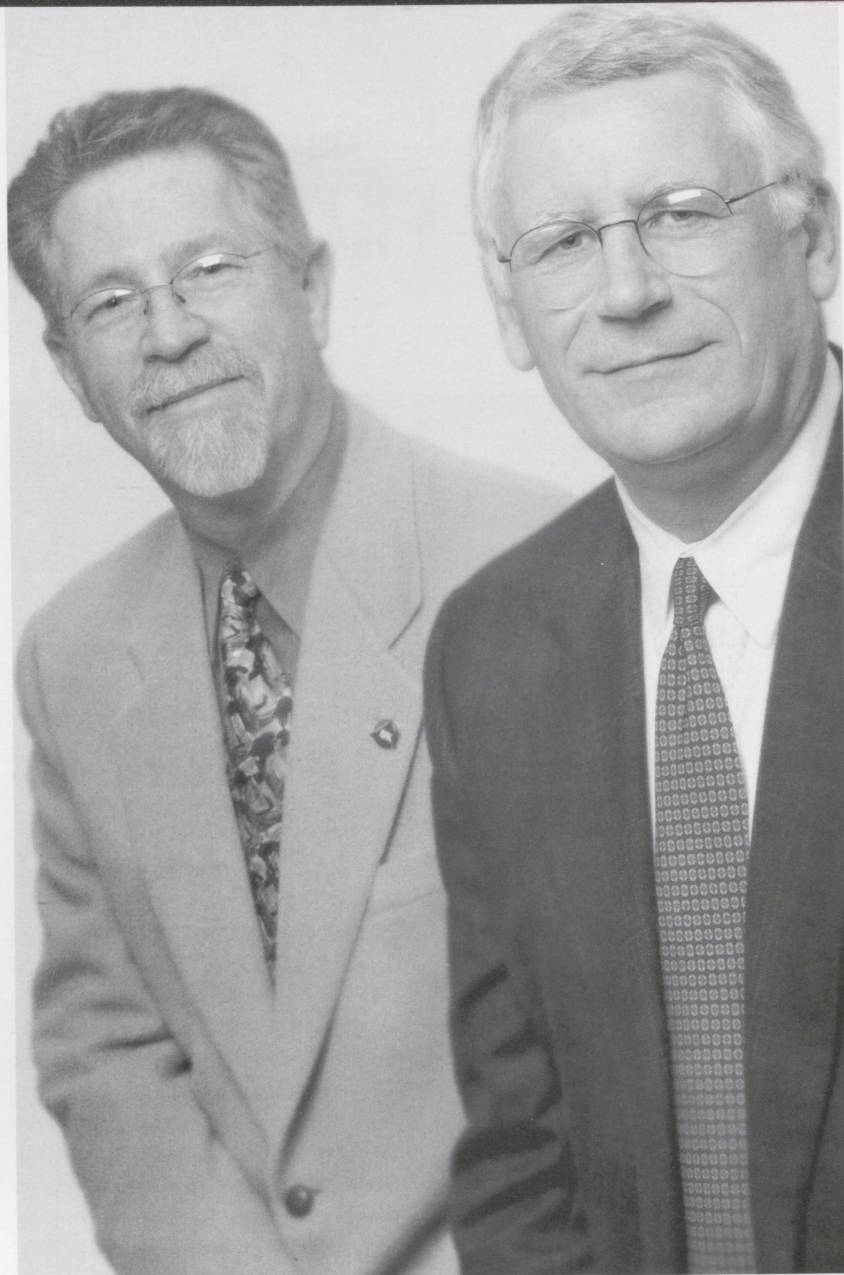
A Little Help from Baboons

In collaboration with the University of Texas Health Sciences Center at San Antonio and The Forsyth Institute in Boston, Ebersole is attacking the problem from another direction, too. He is studying samples from pregnant baboons.

"Baboons were chosen for several reasons," Ebersole says. "They develop periodontal disease similar to humans, they are a tough animal, the mother/child bond is stronger than with many other primates, and there is an available colony of about 3,500 baboons at the National Primate Research Center in San Antonio."

Ebersole and his collaborator, Lakshmya Kesavalu, a veterinary researcher at UK's Center for Oral Health Research, are studying the effects of periodontal disease on pre-term birth in the animals.

Research began in July 2002, with samples from a group of 37 baboons. Ebersole will be making three or four trips to San Antonio each year during this project to collect clinical, microbiological and blood samples. The blood samples will then be brought to UK for study. Ebersole expects the study to be completed in 2007.



Mothers-to-Be Take a Research Role

Ebersole's UK colleague John Novak, professor and associate director of the Center for Oral Health Research, is the principal investigator at UK for a \$7 million study, a human-subjects counterpart to the work Ebersole is doing with baboons. In this first-ever national, multi-center study, Novak and his team will examine pregnant women who already have periodontal disease in a project being funded by the National Institute of Dental and Craniofacial Research.

Jeffrey Ebersole (left) and John Novak in the College of Dentistry are investigating the link between periodontal disease in expectant mothers and low birthweight of their babies. In previous studies, other researchers found that expectant mothers with periodontal disease may have a three- to seven-times greater risk of giving birth to premature and low-weight babies.

“Our goal is simple: we want to help make it possible for mothers to give birth to healthy, normal babies.”

—Jeffrey Ebersole

Delta Dental Ensuring Further Clinical Research

The Delta Dental Plan of Kentucky Clinical Research Center was created in October 2002 with a \$750,000 endowment from Delta Dental, an amount matched by the Kentucky Research Challenge Trust Fund. The center will combine the expertise of medical and dental researchers with research groups around the country, and will serve as a focal point for interdisciplinary research.

The University of Louisville received a similar gift, boosting Delta Dental's investment in oral health research in Kentucky to \$1.5 million. At UK, the center will be the clinical arm of the Center for Oral Health Research, which Jeffrey Ebersole directs.

“The establishment of these centers immediately gives us a greater opportunity to develop and implement collaborative clinical and translational research with investigators in Kentucky, across the country and around the world,” Ebersole says.

The University of Minnesota is leading this study, with research partners at UK, the University of Mississippi and Columbia University. Each university is recruiting 200 patients into the study. Half of the mothers will be treated for periodontal disease during their second trimester and the other half treated after giving birth.

At UK, the research is being done in collaboration with the Department of Obstetrics and Gynecology's High-Risk Maternal Fetal Medicine Clinic. James Ferguson, department chair of obstetrics and gynecology, is a co-investigator on the study. It is the first large, federally funded study to be done as part of the new Delta Dental Plan of Kentucky Clinical Research Center located in the College of Dentistry.

“This is primarily an intervention study,” says Novak. “We will be treating periodontal disease as an infection, then seeing what effect that has on the delivery of the child relative to the adverse outcomes that are associated with pre-term delivery.” He says the primary question is, “Does the mother deliver prematurely?” The secondary question is, “What impact does it have on the baby?”

The researchers began recruiting patients in March 2003 for the study, which will take two to three years to complete. “What we really don't understand is what types of oral infection are associated with pre-term birth,” says Novak. “Is every woman who has an infection in her mouth, who has plaque in her mouth, liable to deliver her baby pre-term? Well, we know this isn't true. Most women deliver normally. So we are also very interested in the types of

infections that make up their dental plaque and the types of bacteria that are colonizing their mouth.”

Novak is targeting seven or eight bacteria, the same ones implicated in many other problems. Interestingly, one of the oral bacterial species may be associated with early fetal loss in horses, a condition called Mare Reproductive Loss Syndrome. Novak and Ebersole are also planning collaborative studies with the College of Agriculture's Department of Veterinary Science to look at the potential contribution of oral infections to fetal deaths in horses.

“Veterinarians have identified a specific organism in the horse that is very closely related to an oral organism in humans,” Novak says. “They don't know how this organism gets from the horse's mouth to the fetus and may create this problem, but they have already isolated the organism from the fetal membranes.”

Novak says this organism, a member of the bacterial family *Actinobacillus*, is closely related to an organism in humans that causes severe periodontal disease in young people. “It appears that similar biologic processes may be occurring in some pregnant mares,” he says.

Ebersole reiterates that the overall goal in his study and Novak's is to identify if there is a link between periodontal disease and pre-term, low-birthweight infants and, if so, how strong this link is. The next step, he says, is to intervene in that process to lower the risk of pre-term birth. “Eventually we hope to have this treated as a public health measure so that every expectant mother receives dental care as part of her prenatal care,” he says. ■

Oral Health and Aging

Infection, disease and aging are inextricably linked in the human health chain, according to John Novak, associate director of the Center for Oral Health Research at UK. He says infection and disease can affect the aging process, and the reverse is also true. "If you get a lot of infections, your body is constantly being stressed, and that may have an impact on aging. Conversely, the aging process itself may affect your susceptibility to disease," he says.

Backed by a \$1.5 million grant from the National Institute on Aging (NIA), and in collaboration with researchers at the University of Maryland and the NIA, Novak is examining the role of infection and oral health in the aging process. In this work he and his colleagues are using Rhesus monkeys located at the NIA facility in Maryland.

"We're using the oral cavity as a model to allow us to study infection, inflammation and disease by looking at aging primates on a lifetime calorie-restricted diet. Calorie restriction has been clearly demonstrated to decrease the aging process in rodents, and now these studies are being extended to non-human primates before progressing to human studies," says Novak.

The first thing he is looking for is whether these animals have fewer infections and less disease than animals that don't have such calorie restrictions. Then the researchers are going to analyze how these



animals respond to infection that leads to inflammation in the mouth and consequent periodontal disease. "Will those calorie-restricted animals, who are not aging as rapidly, respond better than those aging at a normal pace, and how does aging affect the inflammatory response and the disease process?"

Jeffrey Ebersole, director of UK's Center for Oral Health Research, and Karen Novak, John's wife and an associate professor of periodontics, are collaborating on this study.

"People continue to look for aging mechanisms and try to find a magic bullet to prolong life," John Novak says, "but very few people have looked at chronic infection and inflammation as a package contributing to the aging process. We know that as people age, they are susceptible to more infections and certainly the infections and inflammation can put a stress on your body that may lead to premature aging.

"We are excited because we think we will have some major findings to contribute. With collaborative research, you broaden the impact by bringing together a wider range of expertise, and fresh ideas and perspectives."

New therapy
helps adults
process
childhood
sexual abuse



Putting Away the Past

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

inda lost her job over a pack of gum.

Each time her boss popped a stick of Big Red into his mouth, he became her grandfather. That simple piece of gum was a trigger that sent her right back to age eight and the nightmare of sexual abuse she endured at her grandfather's command.

This is just one of the devastating stories Kate Chard can tell. "Childhood sexual abuse affects a man's, a woman's entire life," she says. "We focus on some core areas in my therapy of safety, trust, power and control, self-esteem and intimacy. Those things impact ability to work, ability to sustain healthy relationships, and ability to parent.

"We see anger, fear, depression, post-traumatic stress disorder (PTSD), and a tendency to re-experience. When triggered by an event, person or smell, these abuse survivors often disassociate. They're at work, they've got a child at home, they've got friends around, they're having a hard time maintaining their own connection with reality."

Chard, an associate professor in UK's educational and counseling psychology department since 1996, designed a highly successful therapy program—11 years in the making—that flies in the face of what she calls society's "don't cry/don't think about it/get over it" mentality. "If you go through a traumatic event, that's the exact wrong advice. Stiff upper lip? No way!"

Chard created her therapy program as a grad student at Indiana University, piloted it on an internship, wrote the grant as a postdoc, and was funded by the National Institute of Mental Health (NIMH) as soon as she arrived at UK.

"It was the first NIMH-funded treatment outcome study on childhood sexual abuse," she says. This three-year study of women (Chard has done an equivalent study with men) took adult survivors of childhood sexual abuse through a 17-week, manual-based program, with individual or a combination of individual and group sessions, centered on cognitive processing.

"What you think affects what you feel, which, in turn, affects what you do," Chard says, summing up the basic theory behind cognitive therapy. "We build on this by saying that due to the traumatic event, the ability to process cognitively has become impaired. Biologists can look at the neurotransmitter connections in the brain and actually see differences between people who've been through traumatic events, such as childhood abuse, and people who have not."

While she doesn't do any brain mapping herself, Chard says this altered biology makes sense based on the fact that, as

children, we are only just beginning to conceptualize the world by organizing experiences into categories. She gives this analogy, which she uses with her clients: "You see a two-year-old run up to a dog and say, 'Doggy!' And then she sees a cat, and she doesn't have a schema for cat yet, so she says 'Doggy!' Mom says 'Kitty,' but everything four legs and furry is doggy until the child develops more categories.

"And then I look at my clients and say, 'Where's the category for child abuse?' When you're five, there isn't one. The brain doesn't have a place to store that kind of event, so it ends up bouncing around—not stored well at all in terms of a past, processed event. So what we do in therapy is bring it up, process it, make neurotransmitter connections, make sense of it with a new schema, and put it away."

The first step to "putting it away" is dredging it up, in as much detail as possible, but Chard says she purposefully designed her therapy to make this process less painful. Most therapies start with a recapitulation of the event as a first-person, present-tense verbal account, which makes the victims feel like it's happening all over again. In contrast, Chard's program allows them some distance by putting the account down on paper, in past tense.

"They write it at home, and then they come in and read it to me. There's something far less traumatizing in allowing them to hold onto that piece of paper and distance themselves from the abuse," she says. "When you compare our therapy to others, we show far fewer dropouts."

Of the 36 women who started the therapy, only one did not complete the 17 weeks. Chard contributes some of this success to the ability to lay out a clear treatment plan for clients from the start.

"If you were going in for cancer treatment and your doctor told you, 'I don't know how many sessions I'll treat you with, and I'm not necessarily sure of what I'll do next week,' you'd never go back. Cognitive processing therapy is built heavily upon informing the client of what we're going to do, what side effects they can expect, what the outcome's going to be, and what their obligations to the therapy are."

There's lots of homework: writing up the event and completing worksheets to discuss at each session (like the "ABC sheet" that has you write down what happened today, what you told yourself, and how you felt). "It's time-intensive," Chard says. "That's what we tell our clients. You're going to feel worse before you feel better, but you need to be able to put yourself first for 17 weeks."

Graduate Therapists

This study was unique in that all of the therapists, besides Chard herself, were graduate students. "I think that's one of the neatest things about my therapy because it says you don't have to have years of experience to be a good therapist for childhood sexual abuse survivors. You just have to be trained in using a model that works."

Chard's NIMH grant supported eight doctoral students who had already completed their therapy practicum training. The students sat in on group therapy sessions and watched videotapes of Chard doing the therapy with clients. "After they watched one client all the way through and had been involved in the group supervision for a few months, I assigned them a client and they began videotaping their own sessions," she says.

"I had a few clients who were reluctant to have a junior therapist, but I explained that they are getting my therapy." She pulls out a two-inch-thick, spiral-bound manual. "It's very concrete what they're going to do and what they're going to say. And I'm overseeing their work by watching their videotapes."

Gina Owens, a student who has worked closely with Chard and is in the process writing up her dissertation data on the cognitive processing therapy, says the videotapes are invaluable. "It's a really good tool for learning, particularly when you're just starting out. You have on paper what you need to do during a session, but it's great to have a visual representation of that, just to see how it might play out. It's neat to watch the different questions that come automatically to Dr. Chard because she's done this for so long. It helped me see different avenues I could pursue with clients."

After the students work with two clients, the students become certified therapists. "That was something I built into the grant that the federal government agreed with," Chard says.

"Our dropout rate is the best in the nation, but so is our success rate at treatment completion and one-year follow-up. We have the best numbers for removing symptoms of PTSD, depression, and cognitive distortions of any therapy for adult survivors of childhood abuse."

This kind of cognitive processing is effective for all types of trauma (natural disaster, combat, rape, gunshots) but is particularly effective for childhood sexual-abuse survivors, Chard says, because their worldview is tied up in the event.

"We do recapitulation—have them re-experience the event—but we immediately tie that into the cognitions that were developed due to the abuse, and then we empower the client to choose to change those cognitions."

These cognitions—our beliefs and perceptions—play a key role in shaping our worldview.

"You and I developed healthy friendships with peers and parents, and we developed some healthy cognitions, so even if a trauma happened to us later, we had a healthy base that allowed us to be less impaired by the event. For childhood sexual abuse survivors, because the abuse happened during the time when they're developing their schemas about the world, they have a tendency to overgeneralize—everything becomes skewed by this event," Chard says.

"In therapy, we use the client's own information to provide healthy doses of evidence that contradict these overgeneralizations. For example if she says to me, 'All men will hurt me,' I ask, 'When you came to my office, did you pass any men in the hall-

way?' The answer's 'Yes,' and I say, 'Did any of them hurt you?' 'No.' 'Well then, what does that do to your rule on all men? Can we change it to some men?' I've just inserted a little bit of evidence."

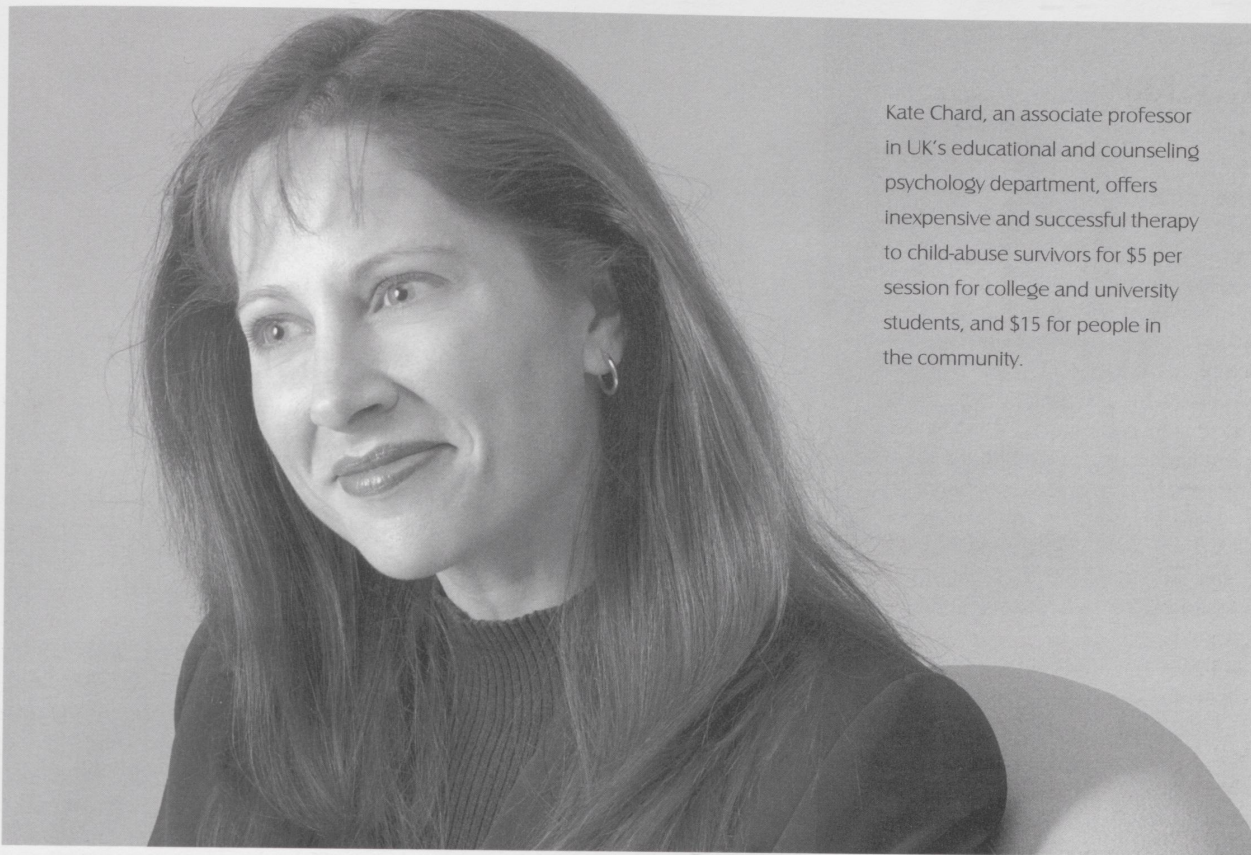
Chard estimates that 60 to 70 percent of the women in her study had tried therapy before. "Sadly, the person who had been in therapy the longest, 15 years, had tried many therapists in town and never felt she'd made progress dealing with her abuse," she says. "We had women ages 18 to 72. There's no difference in terms of severity of symptoms related to age. Childhood abuse persists."

Chard says the thing that gets the most attention from her peers when she makes presentations at conferences is her treatment's success in banishing personality disorders.

"The data I've collected shows a large number of personality disorders 'removed themselves' at the end of therapy. A lot of people say to me: 'You think you can treat a personality disorder in 17 weeks—that's unheard of!'

"I don't think these people have what I'd call a true personality disorder to begin with. I think what we see in trauma survivors, childhood trauma especially, is that they have maladaptive coping skills. The skills they developed to adapt to that dysfunctional, abusive environment become maladaptive as people grow older and deal with society-at-large, and then they get diagnosed as having a personality disorder."

By building coping skills, Chard found that these so-called personality disorders disappear, and she says



Kate Chard, an associate professor in UK's educational and counseling psychology department, offers inexpensive and successful therapy to child-abuse survivors for \$5 per session for college and university students, and \$15 for people in the community.

that impacts the whole landscape of treatment.

"My clinician colleagues often base their mode of treatment on whether or not the client has a personality disorder, and that determines hospitalization and medication. What we're finding is that we don't need to put the person in the hospital; often we don't need to add medication. What we need to do is build coping skills through solid therapy."

Chard says the "Push Me-Pull You" from Dr. Dolittle is a good example of the behavior of someone with maladaptive coping skills. "These people very much want to feel connected and loved, but often as children when they would run up to the mother or father to get this love, they were rejected," she says. "Now as adults wanting attention, they run forward to a friend or spouse, and as that person comes forward they

get scared that something negative's going to happen so they run away. And so, the friend or spouse doesn't quite understand why this person who says she loves you is constantly pushing you away."

Maladaptive coping skills often manifest themselves in avoidant behavior. As Chard says, "When a situation gets sticky at home or on the job, there's a tendency to avoid negative feelings. Survivors associate negativity with punishment or sexual abuse, so they avoid people, places or things that will be triggers."

Linda, whose boss just happened to chew the same brand of gum as her abusive grandfather, couldn't work with her boss because she'd flash back and couldn't function. She ended up getting fired. "It's hard to imagine for people who don't trigger, but for sexual-abuse survivors this is an everyday, if

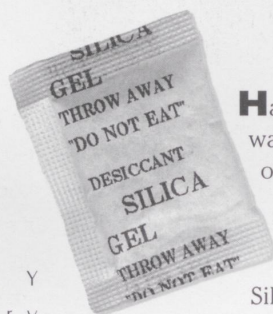
not every hour, experience," Chard says. "But with my therapy we didn't have a single case of someone who didn't get better if they did the homework."

"Every few months a client tells me that her entire life has been turned upside-down, in a good way, because of this therapy," she says. A woman from Madison, Indiana, drove two hours to Lexington once a week for therapy. "I get holiday cards from clients seven years later saying their life is still great."

"I'm not saying I cure everything the client brings to therapy. There are often some marital issues that come up that clients choose to work on in additional therapy, but in terms of the core obstruction of their daily living, we're taking care of removing most of those problems. I can't think of a greater reward than that." ■

Under Pressure

UK scientists create tomorrow's materials with pressure, CO₂ and fluorinated surfactants²



WRITTEN BY
Alicia P. Gregory

Have you ever noticed those little paper packets hiding under the wads of crumpled tissue paper in a box of new shoes? You know, the ones that read: Silica gel, Throw Away, DO NOT EAT.

As a kid, I always wondered what would happen if I tore off a corner and popped one of those spheres into my mouth. Now I know.

Silica gel is hydrophilic—it likes water. Through the science of adsorption, the process by which molecules of a liquid or gas contact and adhere to a solid surface, the moisture gets bound to the silica, averting musty wingtips, or, if you deviantly swallowed it, shriveling you up into a dusty corpse like some character in a bad sci-fi flick.

Okay, that second scenario's an exaggeration—it'd take more like a shoebox full of silica gel to cause dehydration—but it brings up a good point. Adsorbants like silica gel can work only as long as they have available surface area. For example, in gas masks the concentration of contaminants will eventually "use up" the adsorbant—activated charcoal.

The surface area of these adsorbants is made up of millions of nano-sized pores. Nanoporous materials offer exponentially more surface area to which molecules can bind. Silica gel typically contains 500 to 1,000 square meters of accessible surface per gram. (In comparison, the area of a basketball court is 420 square meters.)

Scientists around the world are exploiting the power of adsorption by tailoring porous ceramic materials (made primarily of silica) for a number of important applications: catalysis (facilitating chemical reactions), size separation (filtering and capturing molecules based on their size and chemical affinity), and, eventually, thin films. The molecular-level scale of these thin films (1 to 10 microns thick) can significantly alter the way that molecules in air or in liquids interact with a solid on which they are deposited. The long-term applications for these films will be diverse and may include electrical insulators in microelectronics, molecular-level filters, specialized optics, ultra-thin thermal insulation, and miniature biosensors.

But how do you make these porous materials? At the University of Kentucky researchers are using something no one else has tried—a substance called fluori-



nated surfactant—to synthesize new ceramic materials with nano-sized pores. The four-year project is part of the National Science Foundation's Nanoscale Interdisciplinary Research Team (NIRT) initiative.

"Most organic materials contain carbon with hydrogen bonded to it," says Barbara Knutson, associate professor of chemical and materials engineering, and a partner on the NIRT project. "In place of the hydrogen, you put fluorine atoms and give the molecules different properties."

"What's unique about these fluorocarbons is that they hate both oil and water," says Steve Rankin, a chemical and materials engineering assistant professor, and the principal investigator on the NIRT grant. "When fluorinated surfactants are placed in water or oil solutions, they look for like molecules, and they end up assembling with each other."

Fluorinated surfactants (a surfactant is a chemical that acts as a surface active agent—an emulsifier, surface wetting or repellent agent) are used in all kinds of things: non-stick pans, dry cleaning, cosmetics, electronics, paper products, and plastics.

"A unique property of fluorinated

species is that they dissolve in pressurized CO_2 . So a fluorinated surfactant contains something that is CO_2 -philic, likes CO_2 , linked to something that likes organic or water molecules," says Knutson, who specializes in putting pressure on CO_2 .

CO_2 is a colorless, odorless gas present in the environment. Knutson exploits the solvent properties of CO_2 (its ability to dissolve other substances) at elevated pressures and temperatures, where CO_2 has "supercritical" properties. "Every fluid has a state where it's not a gas or a liquid, but has a combination of gas and liquid properties. That's what we call a supercritical fluid. It has some nice properties of gases—the molecules move around quickly and there's rapid equilibrium. And it has advantageous properties of liquid—it's dense; liquid can hold a lot more than gas."

What kind of pressure are we talking about?

"If atmospheric pressure is in units of one atm (atmospheres), we usually conduct supercritical CO_2 experiments in the range of 75 to 250 atm," says Knutson. This kind of pressure requires special equipment including a view cell (see picture on next page).

Steve Rankin and Barbara Knutson in chemical and materials engineering are using something no one else has tried—a substance called fluorinated surfactant—to synthesize new ceramic materials with nano-sized pores.

Knutson's instrument, which she describes as the "to-die-for" view cell, is one of very few in the country in an academic setting. That's because of the cost. A view cell with all of these bells and whistles (temperature control, pressure settings, mixing, density and viscosity measurement) runs about \$290,000.

So what are supercritical fluids good for? All kinds of things, including separating and making chemicals and materials, Knutson says. "The classic example is extraction of caffeine—producing decaffeinated coffee and tea began in the '80s. Since then, the field has evolved because processing at pressure costs money, and it's only worthwhile for high-value products," she says.

" CO_2 is nonflammable, inexpensive, and environmentally acceptable. A number of pressurized gases are better

solvents than CO₂—high pressure ethane, propane and ammonia—but all of these have consequences for health and safety. In addition, the mild processing temperature of supercritical CO₂ (about 35° C) allows us to work with temperature-sensitive molecules, like biological molecules,” Knutson says.

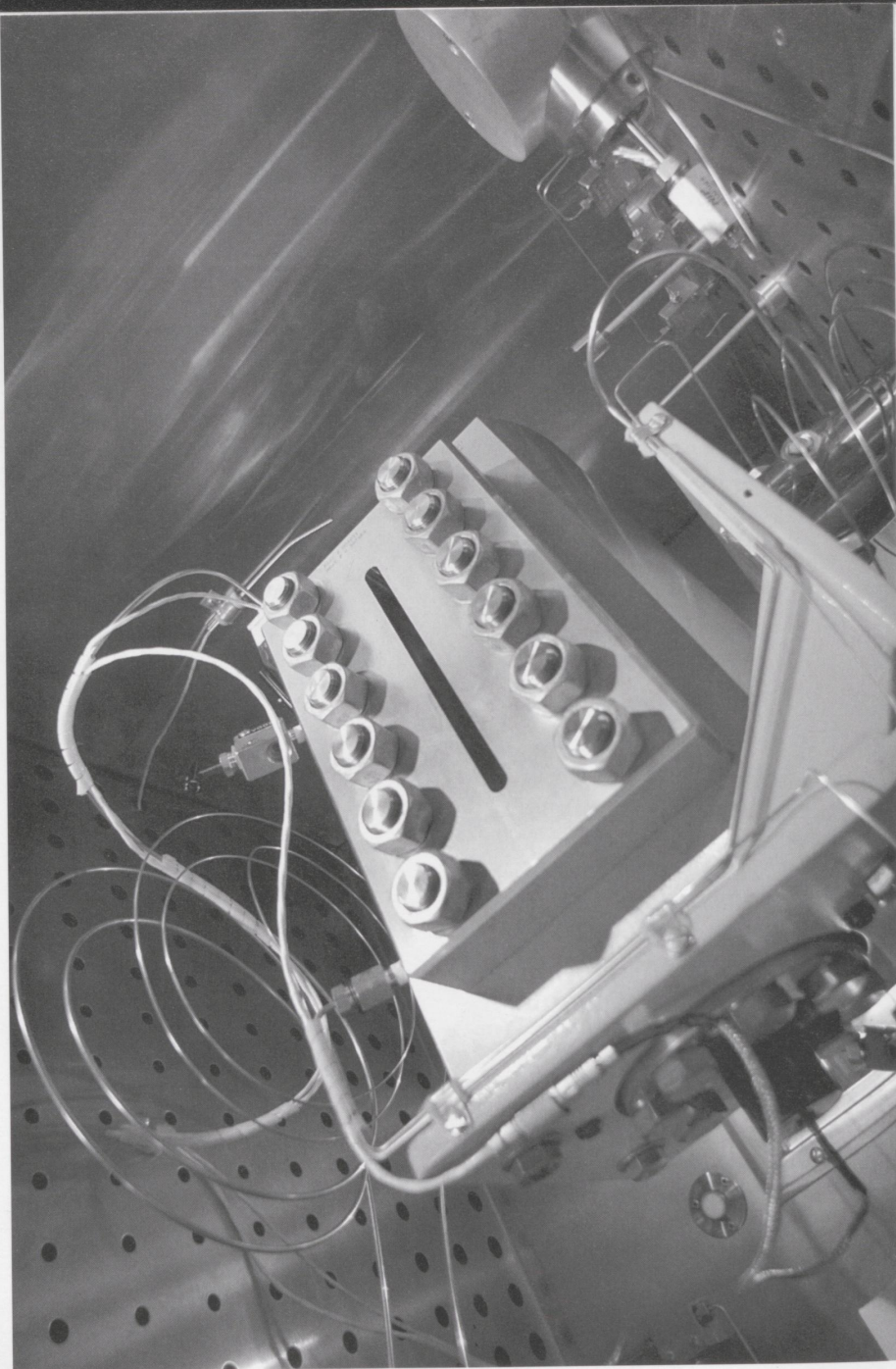
“Residual solvent is an issue in manufacturing pharmaceuticals. Solvents can contaminate the water used in biotechnology and pharmaceutical processes, as well as the product. Working with a non-contaminating solvent is a main theme of my research. We take the pressure off, and the solvent is gone,” she says.

By changing temperature and pressure, Knutson can “tune” CO₂—change how much of a reactant it can hold, how much of a product is soluble, make something drop out of a solution, or—like a scientist-turned-magician—make the solvent disappear from the products.

In the NIRT project, the researchers are basically mixing together water, components that make silica, alcohol, and the fluorinated surfactant. The surfactant binds to itself (a process called self-assembly) forming tiny geometric structures, such as spheres, cylinders, discs, and complex 3-D networks. Pressurized CO₂ is then used to extract the surfactant.

“Wherever the surfactants were, there are now pores, and everything else has polymerized, becoming a solid material,” Rankin says.

“Other scientists have tried to use CO₂ to remove surfactants from their materials, but CO₂ doesn’t really like



“This is our version of a beaker,” Barbara Knutson says. Her pressurized experiments require this view cell. Inside the cell are several sapphire chambers and an outer layer of water. This high-end view cell costs \$290,000.

surfactants unless they're fluorinated," Knutson says. Most scientists remove surfactants by burning or leaching them out with acid. Both methods can alter the fine structure of the newly created material.

The NIRT project began as a brainstorm. Rankin, Knutson, and Hans Lehmler, an assistant research professor in toxicology, were talking about applications of fluorinated surfactants when, in what Knutson calls "a light-bulb moment," Rankin tossed out an idea about a new way to synthesize nanoporous materials. His concept extended the self-assembly ability of traditional hydrocarbon surfactants to fluorinated surfactants, which have the potential to form smaller and more regular structures.

"We have a strong collaborative team with expertise in making the surfactants, understanding their behavior in solution, and synthesizing novel ceramic materials. The work is going very well," says Rankin.

Rankin's team, including five graduate students, is involved in creating better computer simulations that will predict the way molecules will assemble. Then the team will carry out the final step of taking the surfactants and making the materials. Lehmler is designing the surfactants themselves. Using special pressurized tools, Knutson and her students are testing how surfactants assemble and identifying what their phase behavior is (between the liquid and gaseous states), how they will interact with surfaces, and how to get the surfactants out of the material. Every two weeks everyone on the NIRT project meets to share findings and

brainstorm new ideas.

"The great thing about making materials with fluorinated surfactants is, it gives you materials that have a very well-defined and ordered structure to the pores themselves," Rankin says. "All the pores are the same size." Fluorinated surfactants also assemble more easily than regular surfactants into interesting and useful shapes like cylinders, discs and large flat sheets.

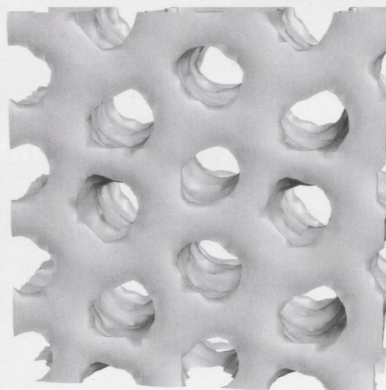
"Some of the original materials people made had pores between 3 and 30 nanometers. The first materials we've made with the fluorinated surfactants have pores that are smaller than that—more like 2 nanometers," he says.

Rankin and Knutson say one application they're very interested in is developing new approaches to making sensors, specifically for the detection of chemical and biological agents.

"We are just getting started in that area, but there are some definite advantages to these fluorinated materials—having defined pore size and being able to put specific chemicals inside those pores that will selectively attract and hold something we're trying to detect," Rankin says. "The process of extracting the surfactants with CO_2 is gentle enough that we can incorporate organic components that bind specifically to target molecules."

"Biosensors are the future of this collaboration," says Knutson. "And the advantages of our process, which combines CO_2 and fluorinated surfactants, suggest that we will find many other applications in the synthesis of advanced materials." ■

Fluorinated surfactants are used in all kinds of things: non-stick pans, dry cleaning, cosmetics, electronics, paper products, and plastics.



One of Steve Rankin's computer simulations, this 3-D image shows where silica would be found in a porous thin-film material made with fluorinated surfactant. This section of the thin film shows pores aligned perpendicular to the surface of the film.

Prime Number : 22 Million (dollars)

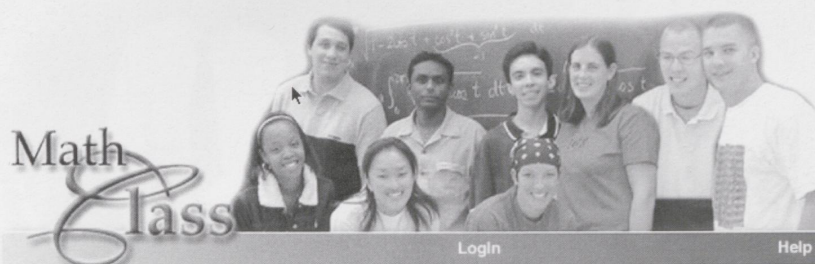
**NSF bolsters
math and
science education
in Appalachia**

"The NSF doesn't just walk in your door every day and plunk down \$22 million," says Wimberly Royster from his office in UK's new Ralph G. Anderson Building. "And in a way it's a challenge. They're saying, 'Here's the money you asked for—now let's see if you can do what you said you could.'"

The five-year grant, which is part of NSF's \$240 million Math and Science Partnership program, is one of the largest single awards in UK's history.

Royster is the project director of this initiative, called the Appalachian Mathematics and Science Partnership (AMSP), one of several projects that will contribute to President George Bush's plan for national education reform detailed in the No Child Left Behind Act. Royster, an emeritus professor of mathematics at UK as well as a former vice president for research, underscores the point that although this award was given to UK, the

Research Outreach



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success of the project totally hinges on the concept of partnership.

"This has to be a team effort," he says, "and everybody on the team has a vital role to play." The players include teachers, administrators and guidance counselors in 52 school districts in Kentucky, Virginia and Tennessee; administrators and faculty at nine area colleges and universities; and various regional agencies. It's a team of hundreds, with a common goal: strengthen and reform central Appalachian students' performance in mathematics and science from pre-school through undergraduate education.

Are students who tackle problems in math and science in these rural school districts not up to par with kids elsewhere in the country? Paul Eakin, the project's principal investigator, believes that there are deficiencies in aptitude and motivation, but that these are not problems unique to Appalachia. "I'd say there are endemic urban/rural realities. But there are clearly unique challenges in educating students in rural areas."

Eakin, a math professor at UK since 1969, says that a quick look at a map of

Appalachia reveals one of these challenges. "The biggest barrier we're facing is geography. Our program will support 12,000 teachers scattered over a 35,000-square-mile area. That's huge. And winter weather in the mountains not only results in many more 'snow days' than in other regions, but also disrupts support and professional development for teachers."

"Because teachers are so isolated, it's difficult for many of them to get to in-service training sites, for one thing," says Ron Atwood, the science program director for this project and the "elder statesman" in the College of Education (he's been at UK since 1966). "The fact that many students in this region 'fall behind' in math and science—what's sometimes called the 'achievement gap'—has to do not only with the geography but also with limited funding for schools and lack of instructional materials. It doesn't have anything to do with the talent of teachers. There are some very capable and dedicated teachers out there."

As AMSP gets off the ground this spring, UK will partner with eight other institutions of higher learning—East-

ern Kentucky, Kentucky State, and Morehead State universities, Pikeville College, Union College, the University of Virginia's College at Wise, the University of Tennessee, and Somerset Community College, along with the Kentucky Science and Technology Corporation—in an effort to supply both pre-service and in-service training, and more consistent and well-targeted course design and development.

"Rural science teachers are difficult to get and difficult to keep," says Eakin. "One thing UK can specifically address through this program is the preparation of math and science teachers. And we want to try to increase the attractiveness of the teaching profession as viewed by our students who come from that region."

Atwood is excited about the new direction UK and the partner universities and colleges will be taking in their content preparation for teachers. "The idea is for all partner higher-ed institutions to have more viable science courses for prospective teachers. And this is the place to address the problem—the most inexpensive place to address the problem."

Research Outreach

By "viable," Atwood means nothing less than a radical shift from the traditional "chalk-and-talk" approach to training teachers to a hands-on approach—a well-planned series of course activities that produce data for analysis and that help students build an understanding of key concepts.

"We need to change our pre-service programs so that teachers are well prepared to approach their students in this way. More hands-on and more '*minds-on*' activities, especially for elementary and middle school teachers in sciences," he says. The idea is for all the higher-ed partners to work on hands-on approaches to teaching math and science, and then pool their ideas. A more effective standards-based curriculum across the partner institutions is the ultimate goal.

Carl Lee, mathematics program director of the project and a professor of math at UK, says another important aspect of the new partnership is a commitment to community and parental involvement. "It's important that a student's parents feel involved, and we want the parents to know what's going on in the classroom and to help their kids with homework."

So how do parents who can't tell a scalene triangle from an ice cream cone help their kids with math and science?

"Well," Lee says, "technology can help with that. And members of the math department here have recently developed a free Web site here in the UK math department—mathclass.org. It's a site parents and their students can log on to and work through homework problems." Lee adds that there's immediate feedback on this site for the re-

"Our program will support 12,000 teachers scattered over a 35,000-square-mile area. That's huge."

—Paul Eakin

sults of student work, which includes the Kentucky Early Mathematics Testing Program to provide on-line testing to help high school students determine their preparedness for learning college-level mathematics. Eakin says that the plan, through the mathematics and science partnership, is to make this available to every teacher in the region, and to students and parents. "We make CDs of whole courses, and recently we've edged into making DVDs as well," he adds.

The need for such a math site arose, in part, out of earlier work that Royster and UK's outreach unit in the Appalachian Center did through a program called the Appalachian Rural Systemic Initiative, or ARSI. "In a sense, ARSI was a precursor to this newer and broader-based NSF program," says Stephen Henderson, who currently directs ARSI, which is housed at the Kentucky Science & Technology Center in downtown Lexington. Over the last seven years this program has helped build a network of schools and a network of support through "research collaboratives"—at UK, the University of Tennessee, Ohio University, Marshall University, and the University

of Virginia's College at Wise.

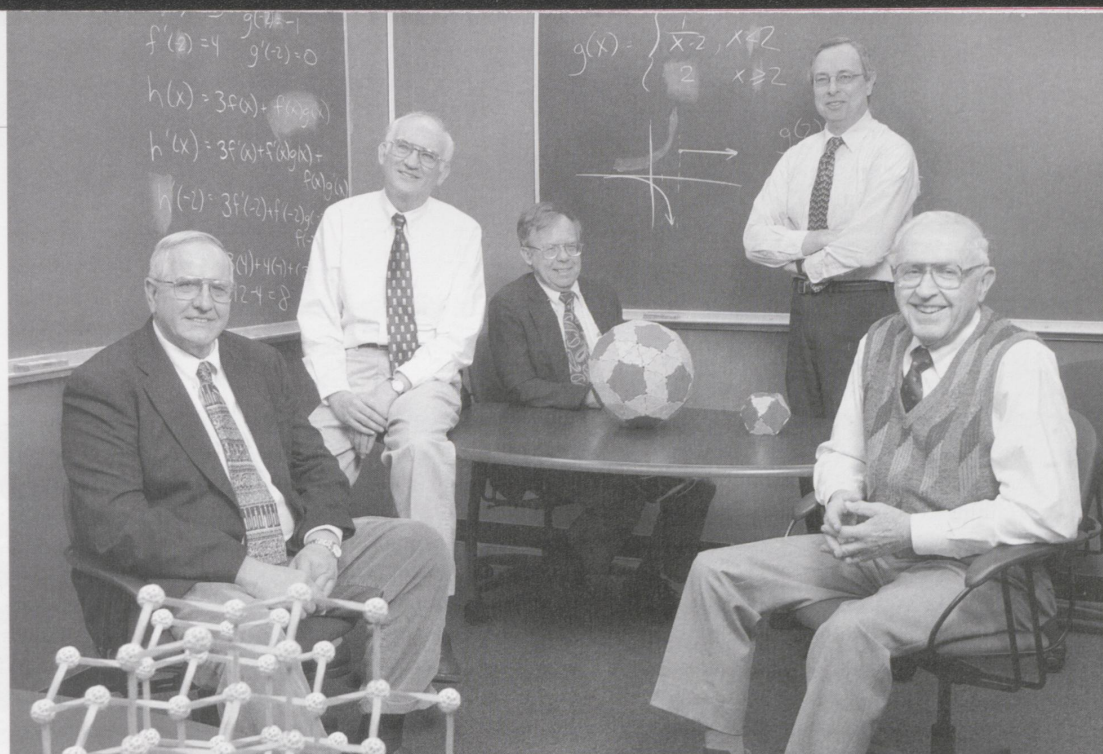
"We've spent an enormous amount of time providing training and support for teachers and instructional supervisors through the ARSI program and now plan to also include principals and counselors in leadership training in the math and science instructional arena," says Henderson. The idea of "leadership training for principals" in mathematics and science might seem a little odd, admits Henderson, who is continuing with the ARSI program and also, now, serving as director of program delivery for AMSP. "What we're doing is trying to show them what they should be seeing when they monitor math and science classes in their school, and how to help teachers improve instruction. The hands-on approach just looks different than what they're used to seeing."

Henderson and Royster emphasize another benefit of the groundwork that's been laid through ARSI—the extensive data they've collected on rural Appalachian schools.

"A major reason we got this larger grant is that we had all kinds of data on these schools. This fact separated us from most of the other institutions that applied for funding," says Royster, who has served as principal investigator of ARSI since its beginning in 1995. Almost all of the data, he explains, supported UK's claim in the grant proposal that significant work needed to be done in these rural Appalachian schools to help students understand—and use—math and science.

Staff from ARSI created a set of indicators to assess how students' performance in math and science aligned

Wimberly Royster (front right) emphasizes the fact that the success of the Appalachian Mathematics and Science Partnership, supported by \$22 million from the National Science Foundation, hinges on teamwork. The UK team includes Royster and (clockwise) Stephen Henderson, Ron Atwood, Paul Eakin, and Carl Lee.



with state standards. Consultants from Inverness Research Associates reviewed 56 schools' assessments in math and science, 19 were assessed in science only, and 21 in math only.

Among the findings were that fewer than half the schools have math and/or science curriculum closely aligned with state standards and that instruction throughout the region lacks an emphasis on higher-order thinking skills—students have little opportunity to engage in serious problem solving in mathematics or inquiry-learning in science.

"One of the conclusions the data led us to," Royster says, "is that to improve instructional practices, better curricula and in-depth professional development are needed, particularly in math. Yet most districts lack the capacity to provide these two critical elements."

"ARSI has had a tremendous impact on our district, from K through 12," says Jennifer Francis, who teaches in a Powell County elementary school. "When ARSI came into our county five years ago, we didn't have formalized curriculum. Teachers were using textbooks in some schools and kits in oth-

ers to teach science. ARSI helped us align our curriculum, and once that was in place provided support with teacher partners to improve instructional strategies and locate resources to support us."

Joe Bailey, who teaches in Whitley County, Kentucky, also applauds ARSI. "We benefited by getting resources at our school in the form of a real, live scientist. Now, through the ARSI contacts, an astronomer comes to our school once or twice a year from the University of Tennessee. We don't have telescopes or that expertise, so bringing him in has benefited our students tremendously." Bailey, who serves now as a math and science coordinator with ARSI, adds that before this program was available in his district, test scores were in decline, and Whitley County was threatened with a state takeover. Since ARSI support has been in place, test scores have started going up. "This year we had five of eight schools meet their goals," he says, "an impressive improvement."

Brenda Edwards, who directs the ARSI Resource Collaborative at the University of Virginia's College at Wise,

Virginia, says, "Just like ARSI, this new and expanded program will benefit the students, and that's the bottom line," she says. "We've collected data on the impact of ARSI, and it's shown us that more than 70 percent of students involved in the program improved significantly in both math and science, 20 percent improved in one or the other, and only three percent showed no improvement at all. Students are also now taking more high-level math and science and doing well in these subjects—and coming to college better prepared."

"The number-one goal as I see it is to get more students interested and excited about science and math," says Henderson. "We have to recognize that it's critical in today's world that young people have a better understanding of math and science, and can make better-informed decisions. From mutated corn raised for pharmaceutical use to cloning to stock-market decisions, we need an educated population. That's my wish. And with the magnitude of this project and the money we have, I think we can make some real things happen." ■



Beware the Shape-shifter

U.S. faces “mad cow-like” epidemic in deer and elk

First it killed sheep. Then it ate cannibals. In the past 10 years, it's created thousands of “mad cows” and warped a rare, age-related brain disease into a death sentence for teenagers who ate British burgers. And today, roaming the wide-open plains of the American West are emaciated deer and elk plagued by this incredibly contagious agent.

Its name: prion (pronounced pre-ahn). Prion proteins naturally exist on the surface of nerve cells in the brain of every human and animal. In most of us this protein never reveals its mongrel potential, but when it does shape-shift into a fiend, it is inevitably fatal.

Glenn Telling at the University of Kentucky is facing this monster head-on in his current research to study chronic wasting disease, the prion protein's deer and elk killer. With grants from the National Institutes of Health, Telling is using basic science to shed some light on the least understood of the prion diseases in animals and trying to

answer the question of whether CWD, following mad cow's precedent, could spawn a disease that targets humans.

Sheep and cannibals

Three hundred years ago a Scottish farmer noticed something odd in his sheep and goats. They were scraping off their wool and hair by rubbing themselves against stone walls, fence posts, anything they could find, as if they were scratching at an itch they couldn't quite reach. Mysteriously, these animals soon suffered premature deaths.

This condition, dubbed scrapie, remained little more than a veterinary curiosity until the advent of a disease called kuru, recognized in the 1950s in a remote cannibalistic tribe, the Fore people in Papua New Guinea. Part of their funeral rituals involved cooking and eating the brains of dead tribe members, but beyond being gruesome, this ritual was killing the Fore.

Carleton Gajdusek, who received the 1976 Nobel Prize for his kuru research,

WRITTEN BY
Alicia P. Gregory

discovered the time from first symptom to death was three to 12 months. In 1959, research veterinarian William Hadlow pointed out the remarkable similarities between scrapie and kuru, namely the destruction of brain tissue characterized by sponge-like holes.

This appearance of brain tissue destroyed by what was later identified as prions led researchers to dub this family of fatal diseases "transmissible spongiform encephalopathies."

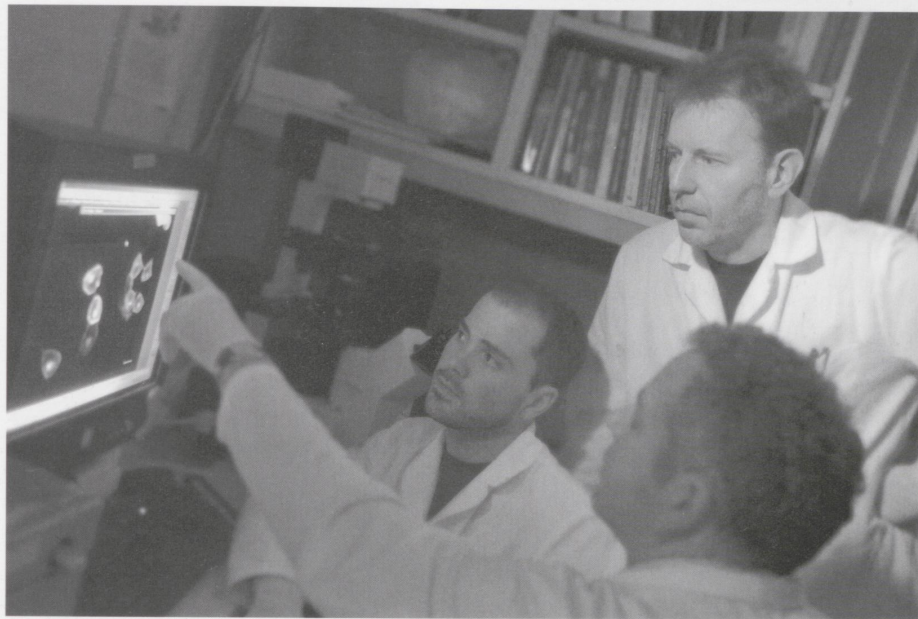
The trouble with proteins

But how do good proteins go bad? The prion protein, PrP for short, can somehow transfigure itself into a pathogen simply by changing shape. As PrP twists, bends and folds, it undergoes a transformation akin to Dr. Jekyll and Mr. Hyde.

The good and evil versions are chemically identical chains of more than 200 amino acids. The only difference in the evil protein—the one that can cause disease—is misfolded sections that take on a flat shape rather than the normal spiral. The rogue, misshapen protein then has the ability to warp other pure proteins into disease-causing shapes, which, in turn, lock together forming long chains that kill nerve cells, riddling brain tissue with holes.

Prions are an entirely different breed of evil. Coined by Stanley Prusiner in the early 1980s, and derived from "proteinaceous infectious particle," the term "prion" marked a new paradigm of infection. Up to that point every infectious agent known to science fell into the well-defined categories of virus, bacteria, fungi, or parasite, and certainly anything infectious had to

Third-year grad student Michael Jernigan, research associate Adrian Centers (pointing) and Glenn Telling (standing) discuss images of PrP, the prion protein, injected with a fluorescent agent that allows the scientists to study living infected cells.



have a genetic component (some DNA or RNA) to drive it. Proteins couldn't be infectious on their own—or could they?

Placing the blame

"Looks like a virus, smells like a virus, must be a virus." Telling says this was the obvious conclusion for scientists searching for a causative agent in scrapie.

But Prusiner set out to test a sensational theory that the infectious agent lacked any nucleic acid (DNA or RNA). His work at the University of California-San Francisco revealed that the prion protein could fold into two distinct shapes (what scientists call conformations)—one normal (PrP^c: the amicable Dr. Jekyll) and one that caused scrapie (PrP^{Sc}: the nefarious Mr. Hyde).

**Deposited by
disease-carrying
animal carcasses,
prions can lurk
in soil for years,
waiting to infect
grazing animals
that ingest them.**

"He was the first to show that to cause disease this protein somehow goes awry, and it appears this happens when it shape-shifts," says Telling, who worked with Prusiner for eight years in San Francisco, first as a postdoc and later as a faculty member.

Telling says Prusiner was regarded as a maverick at the time he proposed his prion theory. "He had trouble getting funding from NIH, and his views were not widely accepted. Since then, Stan has done a remarkable job to convince people, by doing excellent science and rallying the aid of a lot of very smart people." Prusiner's work was further vindicated with the Nobel Prize in 1997.

"Today nobody would argue that, at the very least, PrP plays some role in the diseased state," Telling says. "At one extreme, skeptics contend that it acts as a receptor for some yet-to-be-identified virus. At the other extreme is the protein-only hypothesis, in which the abnormal protein itself is the infectious agent and converts normal pro-

teins into pathogenic ones.

"There are a lot of gray areas in between, which makes this at the same time extremely interesting and frustrating to work on," says Telling. "No virus has been found and no virus-specific nucleic acids have been identified, in spite of exhaustive efforts to detect them."

Some very basic questions about prions remain.

What is their natural function? Telling says that prion proteins seem to play a role in maintaining appropriate copper levels in the brain, but beyond that, scientists don't have many good leads. (Copper helps supply blood to the brain, acts as a brain stimulant, and aids in nerve and brain function.)

Why are they so difficult to kill? Conventional means of sterilization (like cold, heat and ultraviolet radiation) that can successfully inactivate viruses have little or no effect on prions, which Telling says is yet another clue that this is an infectious agent unlike any other. Surgical instruments and lab equipment that may have come in contact with prions from brain tissue or lymph nodes are difficult to sterilize. As a result, European hospitals are using disposable surgical instruments as of-

ten as possible. It takes up to 1,080 degrees Fahrenheit to destroy prions. Deposited by disease-carrying animal carcasses, prions can lurk in soil for years, waiting to infect grazing animals that ingest them.

Why do these diseases take so long to incubate? Incubation periods ranging from months to decades frustrate scientists' efforts to nail down a point of infection. "The long incubation has something to do with the rate of conversion of normal proteins to pathogenic ones," says Telling. "If you are peripherally infected with these agents—say you ingest them—it takes time for them to infiltrate the central nervous system, and then it takes more time for replication and accumulation of prions to levels that cause permanent damage." Symptoms include impaired muscle control, loss of mental acuity, memory loss, depression, insomnia, and emaciation.

Prions don't cause Alzheimer's disease, but prion proteins share similar features with the non-infectious proteins that accumulate in Alzheimer's fatal plaque deposits. Future pharmacological interventions designed to prevent proteins from changing shape may be able to halt this domino effect and successfully treat prion diseases and other neurological disorders.

The prion protein, PrP for short, can somehow transfigure itself into a pathogen simply by changing shape. As PrP twists, bends and folds, it undergoes a transformation akin to Dr. Jekyll and Mr. Hyde.

prion

(pronounced pree-ahn)

Seeing pink elephants

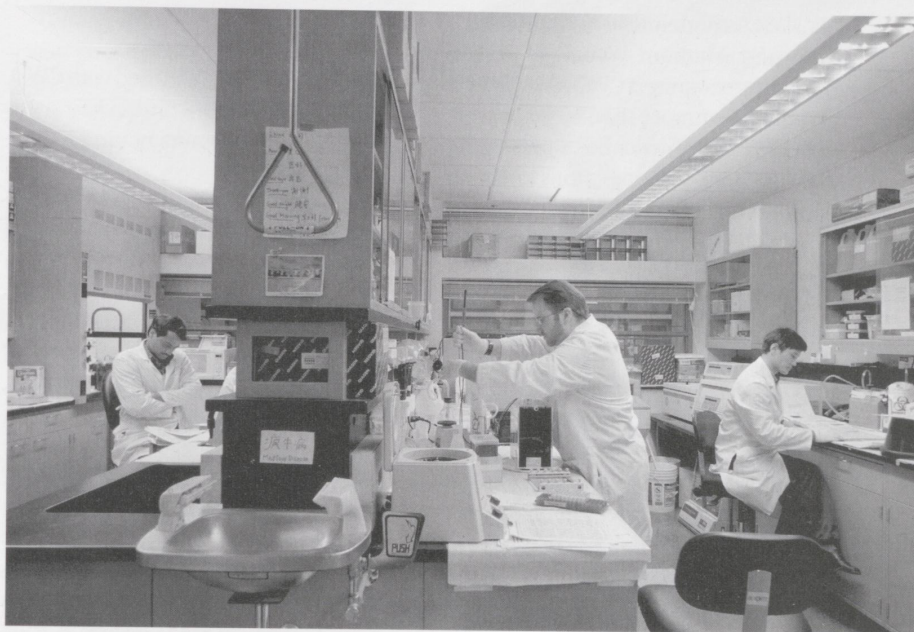
The most common human prion disease is Creutzfeldt-Jakob Disease (CJD). Like Alzheimer's, CJD is normally a disease of old age. It most frequently occurs in people in their 60s. Unlike Alzheimer's, CJD is rare: it kills one in a million people.

There are three types of this disease. The first, sporadic CJD, accounts for 85 percent of cases. Scientists call it sporadic because it occurs infrequently and in scattered cases. The rarest type, acquired CJD, is caused by infection, usually accidentally. Only 250 cases have been documented worldwide of people who developed CJD after medical procedures such as injections of human growth hormone from cadavers, corneal transplants, and infected surgical instruments. The last type of CJD is inherited in families carrying specific mutations in the prion protein gene and accounts for 15 percent of cases.

Between 1994 and 1996, 12 British teenagers were diagnosed with CJD. "To see CJD in people under 30 was the neuropathologist's equivalent of seeing a pink elephant," Telling says.

The timing of the diagnoses eerily coincided with Britain's outbreak of bovine spongiform encephalopathy (BSE), aka mad cow disease. "About 180,000 cattle have been killed by this disease, and recent estimates suggest that a least two million cattle were exposed to the agent," says Telling, a native of Great Britain with firsthand knowledge. Although he did all of his training and spent the majority of his career in the United States, Telling spent two years with the Medical Research

Attacking prions in Telling's lab: (left to right) Rajgopal Yadavalli (a postdoctoral fellow), Shawn Browning (a grad student in the microbiology Ph.D. program) and Jifeng Bian (visiting scientist from Shandong Medical University in China)



Council in London at the height of the epidemic.

Scientists traced BSE back to prions in scrapie-infected sheep. Cattle were fed meat and bone meal made from sheep, and then cattle were fed meal from other cattle. "The disease was propagated by refeeding cattle to cattle in a cyclical process. Basically high-tech cannibalism," Telling says. "In 1996, Britain removed all animals over 30 months old from the food chain and established a ban on feeding ruminant-derived protein to other ruminants [deer, sheep, cows]."

"Cattle are extensively consumed by the general public, so it's likely that BSE prions jumped from cattle to humans via the food chain." Science has since confirmed that this "new variant CJD" is actually the human form of BSE, Telling says. To date, 129 people

in the U.K., six in France, and one in Hong Kong, Ireland, Italy, the United States, and Canada have been diagnosed with new variant CJD.

The threat across the pond

"Could this happen to us?" This is the question facing officials and hunters in North America in light of an emerging disease in deer and elk.

Eleven U.S. states (Colorado, Illinois, Kansas, Minnesota, Montana, Nebraska, New Mexico, Oklahoma, South Dakota, Wisconsin, and Wyoming) and two Canadian provinces (Alberta and Saskatchewan) have reported cases of chronic wasting disease (CWD), a prion disease that causes progressive weight loss, excessive salivation and urination, and inevitable death.

Affecting wild and captive mule deer, white-tailed deer and Rocky Mountain

Eleven U.S. states have reported cases of chronic wasting disease (CWD), a prion disease killing deer and elk.

elk, CWD is endemic in northern Colorado and southern Wyoming. Scientists have recognized CWD as a clinical syndrome for more than 30 years, but the disease may have been present in free-ranging deer populations for more than 40 years. One thing that's clear is that CWD is a highly contagious disease, particularly in captive settings.

Telling has partnered with Colorado State University and recently received a \$2.6 million share of a seven-year, \$8.4 million grant from the National Institute of Allergy and Infectious Diseases, part of NIH. Colorado State's portion will fund an emerging disease research center, in Fort Collins, focused on CWD. This is one of seven centers supported by NIH in a new push to explore emerging infectious diseases.

The Colorado Department of Wildlife facility in Fort Collins has been at the center of CWD research for a number of years. "We know that deer and elk that are introduced into the Fort Collins facility develop CWD at a very high rate," Telling says. "But we don't know exactly how." Scientists speculate bodily fluids like saliva or urine may transmit the disease, and animals that are confined have a greater chance of exposure to other animals. Efforts to sanitize the facility have been unsuccessful.

Shipping deer and elk across state lines for breeding purposes has most likely played a role in the spread of CWD. And it's possible that efforts such as Kentucky's aggressive program to reestablish a free-ranging elk herd in Eastern Kentucky, which started in 1997, may have brought the disease to the Bluegrass. No deer or elk in Ken-

tucky have been diagnosed with CWD, but elk were imported from two states (Kansas and Nebraska) currently battling the disease.

Telling has discussed strategy with the Kentucky Department of Fish and Wildlife Resources, and, according to Jonathan Gasset, wildlife division director, that department, in cooperation with the Kentucky Department of Agriculture and the Kentucky Alternative Livestock Association, created regulations in July 2002 to protect the state from possible CWD infection. In November, Kentucky Governor Paul Patton issued an executive order placing a temporary moratorium on the import or export of deer and elk. Gasset says deer and elk resources in Kentucky contribute more than \$300 million annually to the state's economy through hunting, wildlife viewing and employment related to those activities.

When the CWD threat came to light, hunters were told not to eat organs known to harbor prions, like the brain, spinal cord, tonsils, eyes, spleen, and lymph nodes; and they were warned to wear rubber gloves when processing animal carcasses.

"We don't know if this disease can transmit to other animals, in particular livestock that share pastures with deer and elk in the West," Telling says. "Could CWD cross the species barrier to create a BSE-like disease in cattle or a scrapie-like disease in sheep? And more importantly, we don't know anything about whether this disease will cause problems in humans, and this is a particularly important question in

light of the emergence of new variant CJD in Europe.

"The stakes are a lot higher than 15 to 20 years ago," he says. "The CDC, USDA and NIH are very concerned about this disease because they don't want a mad cow epidemic on their hands."

Mice as a model

One more question in the list of unknowns about CWD is the prevalence of strains. Viruses can manifest as different strains caused by slight genetic variations that result in different biological properties. Prion diseases appear to have similar variations, evidenced by longer or shorter disease incubation periods and differences in severity of symptoms. But how do strains work in prions—without DNA or RNA?

This was one of the questions Telling tackled in San Francisco with Prusiner. "Our work showed that different strains of prions had subtly different conformational states that appeared to correlate with strain properties. The strain of the agent is somehow enciphered within the conformation [shape] of the prion protein, and that conformation is imparted with a high degree of fidelity from one protein to another."

But how do you isolate strains of CWD? Telling's program, supported by grants from NIH, focuses on transgenic mice. He has inoculated these mice with CWD, and is in the "wait and see" stage. (The long incubation period means it will take a while for clinical symptoms to develop and his next round of work to begin.) Telling will compare CWD from deer and elk to look for strain-indicating differences in the prions.

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"This transgenic animal model is important because, for the first time, we'll be able to test the infectivity of various tissues and bodily fluids," he says. "Is saliva the key to how this disease is transmitted from one animal to the next? We can't tell from infected deer and elk," Telling says. Besides the fact that deer and elk aren't ideal experimental models because of their size and expense, the main problem for scientists is the difficulty of maintaining CWD-free control groups.

In addition to making transgenic mice that are susceptible to deer and elk prions, Telling says one future goal of this work is to make use of transgenic mice that are susceptible to human, sheep and cow prions, a crucial step in identifying how prions jump between species. "This will allow us to explore the most important molecular determinants of the species barrier and prion strains. If, for instance, we saw transmission of CWD into mice that normally respond to human prions, it may indicate the potential for CWD transmission to humans."

Pro-active attack

"If CWD were to transmit to humans, we don't know whether it would look like new variant CJD. It could have an entirely different neuropathology and not exclusively affect younger people," Telling says.

U.S. doctors and scientists are looking for CJD more closely than before, he says, but it's a difficult task. "CJD is a rare disease, and it can look a lot like other neurological disorders. It's only definitively diagnosed with a brain biopsy after death."

Telling talks about the much publicized group of Wisconsin hunters who annually feasted on wild game, including elk from Colorado and deer from Wisconsin. Two of the men died in 1993 and the third in 1999; all were between the ages of 55 and 60. All appeared to have CJD and, because of the sheer numeric improbability that this was coincidence, speculation ran rampant that they got the disease from consuming prion-infected meat. "Tests have proven that one of them died from Pick's Disease, a related, non-prion neurological disorder. One of them had an inherited form of prion disease caused by a mutation." The third man's disease could not be scientifically linked to CWD, Telling says.

"Right now there's no convincing evidence that any of these cases in the United States acquired CJD as a result of being exposed to either BSE or CWD prions, but people tend to make those connections easily. Because the stakes are very high, it's important not to jump to premature conclusions."

Telling is seeking \$2.6 million from the Department of Defense for his next study in collaboration with colleagues at the University of Rochester in New York. This study is related to work by Adriano Aguzzi, a pathologist in Zurich, who has made transgenic mice that express a particular antibody and are completely resistant to prion infection.

"His results give evidence that immunotherapy for prions is a possibility," Telling says. "We'll test specific antibodies produced at the University of Rochester to see if those antibodies can protect against the development of CWD using our transgenic models."



Immunotherapy is one of the hottest topics in prion research right now."

This \$2.6 million is part of a \$42.5 million congressional appropriation to the National Prion Research Program, run by the DoD. The military is supporting prion research based on the potential threat to food and blood supplies.

"By being proactive the U.S. government is taking exactly the right approach," Telling says. "CWD is an emerging disease, perhaps the least understood of all of the prion diseases in animals. It's extremely contagious, and it's an open question whether it's going to be a major public health threat or transmit to other animals."

"There are still a lot of unknowns, and it's critical to keep an open mind. It's important to err on the side of caution, in light of the debacle that occurred in the U.K." ■

For more on prions, see "The Blood Threat" online at www.rgs.uky.edu/ca/odyssey/spring03/shapeshifter.html.

2002-2003 University Research Professors

Thomas Leinbach: Bolstering Indonesia's Rural Economy

"Each year 2.5 million people in Indonesia are coming into the labor force, looking for work," says Thomas Leinbach. "About 80 percent of Indonesia's population is rural. So the government is faced with the question: 'How do we create employment?'"

Leinbach, a professor of geography at UK for 25 years, has studied economic development in Indonesia since 1978. His current research explores what he calls an "understudied" aspect of rural non-agricultural employment—how the development of small businesses fits into family aspirations.

"Many rural families in Indonesia, and in the developing world around the globe, need to do more than farm their own land. Some must take off-farm work for survival. Others do it to achieve some upward mobility or to gain income to put their children through school. Many Indonesian children still do not get beyond elementary school."

Leinbach says the government's compulsory education program has been derailed by the economic crisis in Indonesia. "Attendance rates of children in poor families have been especially affected. While over 90 percent of eligible students are enrolled in elementary school, this figure drops to 53 percent for junior high school."

The kinds of enterprises Leinbach is studying include informal transportation and repair businesses, furniture making, garment manufacturing, batik cloth and other handicraft operations. "I'm looking at small businesses that are not associated with agricultural production or processing—things that provide services or produce and manufacture goods, and have an element of entrepreneurship." His research includes analysis of labor participation and census data, as well as face-to-face interviews conducted in Indonesia with successful entrepreneurs and their families to "find out what drives these enterprises."

Women and children play a crucial role in the rural non-farm economy, Leinbach says. "In many cases both the head of the house and the spouse have businesses. Many women operate and manage 'warungs,' a kind of general store that sells everything from cooking oil to rice to tobacco to soap.



There's profit even in such simple and small-scale operations, and these enterprises can be managed while the spouse raises children and carries out other household duties." It's also common for families to send children off to the city to work. "Young girls go into the city as maids or textile factory workers; young boys do apprenticeships in service occupations or factory work."

Leinbach's research in Indonesia has been supported by the University Research Professorship, Fulbright-Hays awards, the National Science Foundation, and the National Geographic Society.

This work has spawned two book projects. The first is *The Indonesian Rural Economy: Mobility, Work and Gender*, a soon-to-be-published collection of original essays to which Leinbach contributed three chapters. He is also working on *The Rural Labor Process in Indonesia*, which, as Leinbach says, "examines family livelihoods through the lenses of mobility, employment activities and the process of entrepreneurship." This book is based on analysis of census data and his own case studies.

—Alicia P. Gregory

Gary Ferland: Configuring Quasars

UK's Gary Ferland, a professor of physics and astronomy, spends a lot of his time in Outer Space—way out in Outer Space.

His research focus for the past 22 years has been the study of quasars—small, intense celestial sources of radiation characterized by large changes in wavelength. The astronomer begins this study by analyzing data downlinked from the Hubble Space Telescope, our eye on the universe that can see billions of light years away with amazing clarity. The Hubble “observes” quasars through spectroscopy, a way of separating electromagnetic radiation according to wavelengths.

Ferland admits the fundamental challenge of such work is numerically simulating what goes on in a quasar. “In astronomy we can’t do an experiment as you can in physics. All we can do is observe what comes to us,” he says. “There’s an old saying in the field: ‘Those who can do, do; those who can’t, simulate.’”

Ferland’s ongoing project involves the development of a large computer program used to simulate astronomical objects like quasars and supernovae. His primary goal is to achieve the formidable task of tracing the birth of the very first stars in the universe. “This happened about 12 billion years ago, and these were near the centers of very massive clouds of gas that were forming quasars,” he explains.

He adds that in the past couple of years he’s been recasting much of his work to be in step with the next generation of NASA’s space observatories. These will, for the first time, obtain very high-quality images and data in types of infrared light that cannot reach the ground. “This is an exciting opportunity to take advantage of observations that were never



before possible. I’ve developed the code’s infrastructure specifically for the types of observations that will become possible.”

Ferland says he is thankful for the University Research Professorship because it has allowed him the unique opportunity to focus all his efforts into making major improvements to the physics, and improving the code itself. “It’s seldom possible to put a great deal of work into basic infrastructure of a project like this, due to the need to get new results and meet deadlines, on top of the other demands on time.”

—Jeff Worley

The University Research Professorships, established in 1976 to recognize outstanding research achievement, carry an award of \$35,000 to enable professors to devote full time to their research or continue to teach and use the award to support research activities. Since the inception of the award, there have been 93 University Research Professors at UK. Funds for this award are provided by the Office of the Vice President for Research.

Andrew Klapper: Finding Structure in Randomness

"It's really an operation that's very much like addition and subtraction. It's very, very simple."

That's how Andrew Klapper, a computer science professor entering his 10th year at UK, describes the process of utilizing the "key" (think encoder/decoder) in private key cryptosystems.

These types of encryption systems, faster but not as secure as those that keep credit card numbers safe on the Internet, help ensure that interlopers can't eavesdrop on large-volume communications like mobile-to-mobile phone conversations or video on demand.

In cryptography, unpredictability is crucial. The idea is that if the coded sequence in which a message is embedded appears to be irregular, intruders cannot easily predict the rest of the sequence and get access to the message itself.

To create this safeguard of unpredictability, cryptologists like Klapper utilize sequences that seem to be random in nature.

"We look for random-appearing sequences and hope that they are also unpredictable," Klapper explains. "These random-looking sequences are then used to scramble messages in unpredictable ways. My interests are in understanding and generating such sequences using algebraic methods."

Yet the full story of Klapper's research in encryption belies the complexity behind the "simple" mathematical concept. Its highlight is his invention of a new class of pseudorandom sequence generators called Feedback with Carry Shift Registers (FCSRs), which he developed with colleague Mark Goresky in the early 1990s.

Klapper's work on FCSRs evolved as a result of successfully attacking a weakness in an earlier cryptosystem that had been used to secure information transfer in the European banking industry.



This is mathematical work that can never sleep, Klapper says.

"There's a constant give and take," he says. "People invent new systems, and then a few years later others come up with ways of attacking them. Then we have to come up with new systems to resist the new attacks."

Klapper will use the 12 months' dedicated research time funded by the University Research Professorship to finalize his first book about FCSRs, tentatively titled *Algebraically Generated Sequences*.

Beyond cryptography, Klapper says FCSRs will eventually have many other applications, most immediately in the field of Quasi-Monte Carlo simulations. This is a widely used approach to modeling physical phenomena with somewhat random behavior, such as the flow of air over a proposed airplane wing design.

The application, though, is not what excites Klapper most. It's the math.

"Finding a proof is the most exciting thing about my work," he says. "I think of myself as a theorist. My goal is finding the theoretical foundations of FCSRs so that people who do the applications can take them and use them."

—Robin Roenker

2002-2003

University Research Professors

Timothy McClintock: Making Sense of Smell

UK physiology professor Timothy McClintock's career in olfactory research started when he decided to accompany some hermit crabs who were house-hunting.

"Hermit crabs live in snail shells," McClintock explains. "And there's no better snail shell than one that was just a snail a few minutes ago. Evolutionally, crabs have learned to detect places where snails are being eaten. When they smell it, they come running."

Working with this smell-mediated behavior as a second-year graduate student, McClintock was hooked. His research—now primarily with mice and lobsters—has been in olfactory reception ever since.

It's a field wide open for discovery.

"You have about 35,000 genes in your genome, and 1,000 of those genes, almost 3 percent, are devoted to olfactory reception," says McClintock, who began his work at UK nine years ago. Moreover, the olfactory system is one of only three parts of the nervous system known to be capable of regenerating.

"The sensory neurons in your nose die and are replaced normally throughout life. They live only 60 to 90 days," McClintock explains. "You have a couple of million of them, so you're talking about replacing 20,000 or so per day. There are also two nerve cell types that are replaced continuously in the brain's olfactory bulb."

Ultimately, insights into how olfactory neurons regenerate may lead to therapeutic applications for neurodegenerative disorders and neurotrauma, McClintock says.

Another key question in olfactory research is exactly how the system takes something as intangible as a scent—which has no definite spatial origin like vision or sound—and converts it into a neural code the brain understands.

"Odor information is more like thoughts and ideas than other sensory information. It's free from a spatial dimension," McClintock explains.

The support of the University Research Professorship has allowed McClintock to do certain costly experiments he wouldn't have been able to do otherwise, he says.



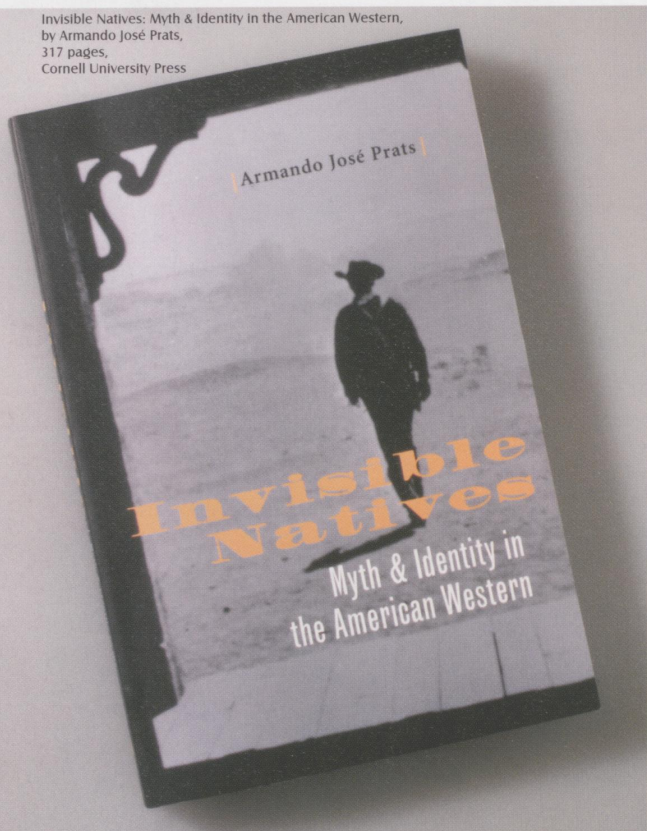
While olfactory biology is a "hot area of neuroscience" right now, McClintock says his UK team's work—focusing on analyzing olfactory receptor proteins and the molecular physiology of isolated olfactory cells that share specific characteristics—is unique in the field.

"One of the fascinating things about smell is that some of its effects on our behavior are unconscious," McClintock says. "That's what the whole perfume industry is based on. I think it behooves us to understand how the sense of smell works. There are plenty of questions still to be answered."

—Robin Roenker

Book End

Invisible Natives: Myth & Identity in the American Western,
by Armando José Prats,
317 pages,
Cornell University Press



Growing up in Havana in the 1950s, Armando Prats began a long love affair with the American Western.

"We were very tapped into America, and my friends and I would go to the movies every Sunday for a double feature—all Hollywood films. And lots of these, of course, were Westerns."

What attracted Prats to the Western early on, he says, wasn't so much the action as the outcome. "Even before I thought of Westerns as genre or formula or myth, I responded to their moral force and focus. In Cuba our leaders—the guys who were supposed to be the good guys—weren't. The president, for one, was a thief and a thug. The Western provided a moral model—evil can have its day, but the good guys eventually win."

As Prats saw more and more Westerns, though, he began to wonder why the Indians were always portrayed as the bad guys. "Even as a kid it was clear to me that the Indians had a culture, too, and it was even older than white culture. What was so bad, I wondered, about people who were merely defending their land and trying to protect their families against aggressive intruders?"

The 1954 film *Apache*, starring Burt Lancaster as the Indian warrior Massai, was a pivotal movie for Prats in his thinking about Hollywood's portrayal. The film centers around the thousands of Apaches shipped off by train to reservations in

Hollywood's Indian

Oklahoma. The Lancaster character bolts the train, gets wounded in a skirmish and, symbolically, rubs a couple handfuls of earth into his wound to help it heal.

"I felt he was so daring and so human," Prats says. "I saw the movie over and over."

Years later, as an associate professor of English at UK, Prats was still troubled by the portrayal of Indians. And when he decided to write a book about the American Western, his theme became as clear as a full moon shining over an Apache campfire—the treatment of the Indian in Hollywood Westerns.

"Now I was looking at Westerns from the perspective of an academic who knows how to ask questions about movies," he says.

His "looking" took four years and involved taking detailed notes on about 90 movies, some of which he researched at home (the UK English department has a considerable collection of films), and some of which he saw when he traveled to the Library of Congress in Washington or to the Museum of Modern Art in New York. "I ended up with 1,000 single-spaced pages of notes," Prats says. "In this kind of scholarship, you have to create your own text, literally, before you can analyze it."

One of Prats's major discoveries, and one that led to his book's title, was that Hollywood's portrayal of the Indian was predicated on the idea that the Indian had mostly disappeared, or was otherwise invisible.

"The Hollywood Western never produced an Indian antagonist more memorable, or more familiar, than the one we never quite see," Prats says. "In so many of these films, it's the disquieting anticipation of an encounter that fuels the imagination of the fearful whites. Smoke signals and feathered bonnets, arrows and lances, faces in war paint half-seen in the forest, the obligatory row of warriors on the distant ridge—these amorphous images and artifacts announce the Indian," Prats says.

He adds that he worked hard to write a book that will interest academics and the general public. "I would like the book to be read as a document on dominant American culture and how it operates."

"Today so many of these movies are accessible," he says. "I'd be pleased if people read the book, went out and rented some of these movies, and screened the movies with my book in mind. I'd want them to really see what previously they only looked at."

—Jeff Worley

Odyssey
Spring 2003

Parting Shots

"SCIENCE IS AN INTEGRAL PART OF CULTURE. IT'S NOT THIS FOREIGN THING, DONE BY AN ARCAINE PRIESTHOOD. IT'S ONE OF THE GLORIES OF HUMAN INTELLECTUAL TRADITION."

—STEPHEN JAY GOULD

"We live in a society exquisitely dependent on science and technology, in which hardly anyone knows anything about science and technology."

—CARL SAGAN

"The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them."

—SIR WILLIAM BRAGG

"ONE NEVER NOTICES WHAT HAS BEEN DONE; ONE CAN ONLY SEE WHAT REMAINS TO BE DONE."

—MARIE CURIE

"THE GREAT TRAGEDY OF SCIENCE: THE SLAYING OF A BEAUTIFUL HYPOTHESIS BY AN UGLY FACT."

—THOMAS HUXLEY

"We keep, in science, getting a more and more sophisticated view of our essential ignorance."

—WARREN WEAVER

"Science is to see what everyone else has seen but think what no one else has thought."

—ALBERT SZENT-GYORGYI

"When I'm working on a problem, I never think about beauty. I think only how to solve the problem. But when I have finished, if the solution is not beautiful, I know it is wrong."

—R. BUCKMINSTER FULLER

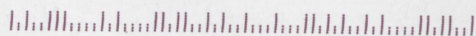
"Science may have found a cure for most evils; but it has found no remedy for the worst of them all—the apathy of human beings."

—HELEN KELLER

Odyssey

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