

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

Clinical



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.

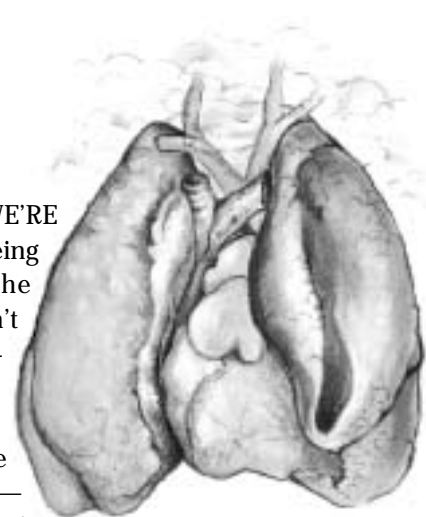
“Kentucky stands out not only as the number one state, but it’s been that way for a long time,” says Timothy Mullett, a lung surgeon and director of the University of Kentucky’s Multidisciplinary Lung Cancer Program. This year it’s estimated that 3,100 Kentuckians will die of lung cancer. “There’s about 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.

Macular 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).

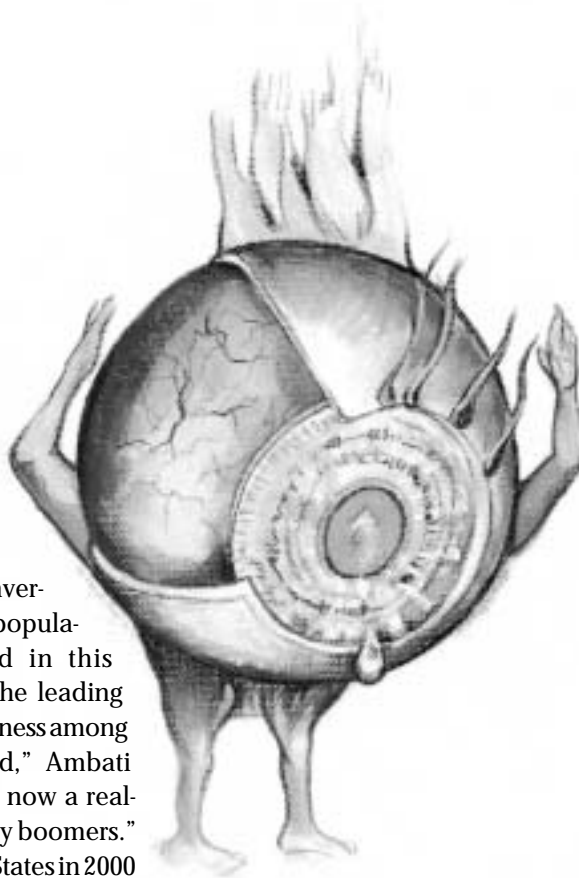
“AMD is the leading cause of blindness not only among the elderly in this and other developed nations, but be-

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

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—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

“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.

Asthma

It takes many researchers some time—years maybe—to find their niche. In Pat Burkhart’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 Burkhart, 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.

Burkhart 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, Burkhart says that blame for increased rates in morbidity and mortality among children with the disease may be a



Patricia Burkhart 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.

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.

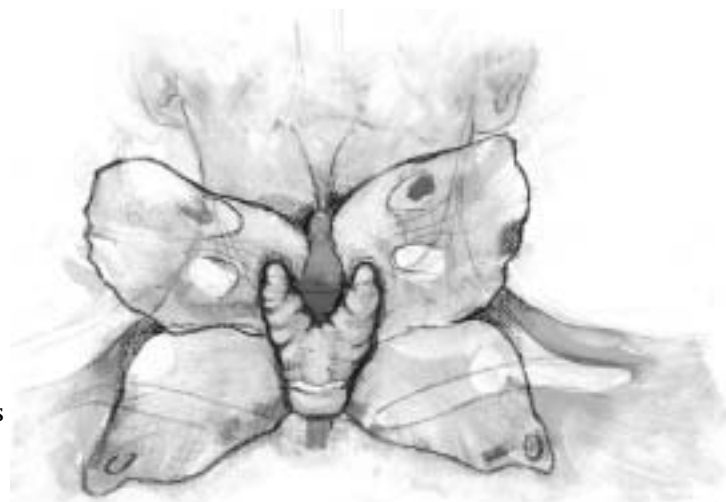
The thyroid gland is situated in the front part of the neck below the skin and muscle layers. This gland is shaped like a butterfly, with the two wings being represented by the left and right thyroid lobes that wrap around the trachea. The function of the thyroid is to regulate the body's metabolism. 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.