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**SCHOOL  
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Achilles McDowell  
Kindergartener at Chenoweth Elementary



# LOST IN THOUGHT

By Jenni Laidman

Photos by Mickie Winters

A groundbreaking Louisville computer-analysis company and the University of Kentucky's Sanders-Brown Center on Aging are teaming up to track Alzheimer's disease in its true infancy.

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**P**ete Nelson is 6-foot-5 with the most regular of facial features: a straight nose, small eyes, a rounded chin, and ears that lie trim to the sides of his head — a face completely in balance. He doesn't smile much today, even if this is the best he's felt in three weeks. That's how long it's been since he threw his back out — the curse, he says, of tall pathologists.

He grabs a white lab coat from his small office on South Limestone Street in Lexington and lopes to the elevator, heading to his first-floor laboratory, where the brains or brain sections of 820 people, most of them Kentuckians, sleep in a dozen tall freezers, waiting for someone to solve their secrets. Waiting for someone like Nelson.

Tom and Nancy Conley's brains will be among these someday. It's hard to picture. Here's Nancy in a pink top, wisecracking in their living room, pantomiming silent commentary to Tom's serious monologue. These days, Tom and Nancy, who live just outside Jeffersontown, are seldom apart. They've always been close, Tom says. Now they are together more often than they have been in 50 years of marriage. Ever since she was diagnosed with Alzheimer's disease, he's reluctant to leave her alone.

It happened in 2008, when Nancy turned 66, the year following surgery, chemotherapy and radiation for breast cancer. After five hours of testing at the Sanders-Brown Center on Aging at the University of Kentucky, where Nelson works, doctors said Nancy's occasional confusion and forgotten lunch dates were indeed significant. She was in the early stages of the disease.

But what does that mean, early stages? It's one of those nebulous terms that hide as much as they reveal. Early compared to what? It turns out, early only in terms of medicine's ability to detect it. But biologically, maybe not so early at all.

Nelson, 46, points to a graph illustrating Alzheimer's progression. This slope would frighten the most accomplished black-diamond skier. Its peak (a mesa, really) marks our many years of normal cognition, when the brain — this little 2½-pound miracle of 86 billion neurons and 400 miles of blood vessels — runs at its seldom-noticed best. But, in Alzheimer's disease, through every passing year, the slope heads downward, until finally, falling at a 45-degree angle, it plummets to death. So far, this is no surprise. But here's the rub: About a third of the way down the slope on Nelson's graph there's a marker that says MILD IMPAIRMENT. Then, almost halfway down the slope of brain failure are the words "early AD." Early Alzheimer's disease. This is the first moment people can be diagnosed, and we're already halfway down the slope of cognitive impairment.

The graph has a second line, this one climbing. It tracks the progress

of the biological hallmarks of Alzheimer's destruction — the so-called plaques and tangles — as they colonize the brain. At that moment of "early AD," this second line is climbing at a 45-degree angle *and has been for years*. By the time the disease is diagnosed, by the time anyone confirms a problem, the poison proteins in the brain are nearly halfway home. Early AD is actually, really, middle AD. The first half, it seems, grows in the dark.

But one Louisville company intends to turn on a searchlight.

A stoic plastic head in the East Chestnut Street offices of Neuronetrix wears strange headgear. Its skull is crisscrossed by black ribbons that lace through 10 white plastic discs. Those ribbons — more like wires — and discs together create a single printed circuit. A chinstrap holds the unit firmly in place, should the plastic head come to harm. It took 10 patents, both issued and pending, nine years, and some \$8 million in investment to produce this simple-looking device, but if KC Fadem, CEO of Neuronetrix, is right, the Cognision system will transform how medicine looks at brain-disease injury.

"I think we're going to identify Alzheimer's at the earliest stages of the disease," says Fadem, 55, whose shaved head gives him a vague resemblance to the plastic model — although the skull lacks the glasses and soul patch.

The device is actually a greatly streamlined, portable and more powerful version of something that's been used in laboratories for years — equipment that can record the brain's electric signals and use them to measure neurologic response. The wearer hears a sequence of tones and is asked to push a button to indicate the highest pitched tone. The electrodes in the white disks on the headset record the brain's electrical activity as it perceives the tone and decides whether to hit the button. That capture is relayed via Bluetooth to a computer, then via the Internet back to Louisville, where it's run through an algorithm that analyzes the complex results and produces a report. "It's a hyper-automatic computer classification system," Fadem says. "There's no need to analyze this crush of data. The computer does it for you. Then the data goes online and ends up in the patient's record."

Even very slight brain changes are evident in the waveforms the Cognision system records. In fact, Fadem once demonstrated that Cognision could detect the boost from a bit of caffeine. Conversely, when the brain loses capacity, even very slight changes are evident to the system, both the longer response times and the recruitment of fewer cells for a given task. Fadem says the device has the potential to detect traumatic brain injury on the battlefield as well as concussion on the football field. The company is talking to college football teams

and the U.S. Marines about using the device to help decide which injured warriors can head back out and engage the enemy. Fadem is also in discussions with several pharmaceutical companies interested in using the Cognision system to test whether drugs that target the brain are making a difference.

“We started looking at different cognitive disorders this technology could be useful for, and Alzheimer’s disease sort of jumped off the page,” Fadem says. Earlier diagnosis of Alzheimer’s could mean earlier treatment. The device is being tested in 1,000 people with mild to moderate Alzheimer’s at seven sites across the country, including the Sanders-Brown center.

Greg Jicha (pronounced JI-kah), a physician and associate professor of neurology at the Sanders-Brown center, is in charge of that trial and several others at Sanders-Brown. You can always distinguish the researchers who also see patients from the pure researchers by their outfits — the men, anyway. They wear ties. Jicha’s tie has tiny portraits of Mickey, Goofy, Pluto and Donald. The other dead giveaway is the stethoscope draped around his neck.

“When people get Alzheimer’s, perhaps even years before plaques and tangles start to form, their nerve cells are sick and not working properly,” he says. Cognision appears capable of picking up even the early degradation. “This is potentially an easy way to detect what we think may be the earliest stage of disease,” he says.

By 2025 an estimated seven million Americans age 65 and older will have Alzheimer’s, a 40 percent increase from the five million with the disease today, according to a study in the journal *Neurology*. In Kentucky, Alzheimer’s is expected to grow by 21 percent between 2010 and 2025 and inflict 97,000 people. In Indiana, Alzheimer’s is projected to rise by 8 percent to 130,000 by 2025.

Behind the higher numbers for Kentucky may be the state’s overall burden of poor health and a slightly higher increase in the number of people 65 and older. Research suggests that Alzheimer’s corresponds with higher rates of type 2 diabetes, high blood pressure, heart disease and stroke — all of which are affected by lifestyle factors such as tobacco use and diet. “Managing blood pressure, diet and smoking — all contributors to vascular disease and heart disease,” says Robert Friedland, a University of Louisville neurology professor who specializes in Alzheimer’s, helps prevent the disease. He also advises regular exercise and flossing. “Inflammation in the mouth,” Friedland says, “is not good for the brain and the heart.” The role of inflammation in Alzheimer’s is a growing research area.

Nationwide, we spend \$203 billion caring for people with cognitive degeneration, a price that could rocket to \$1.2 trillion by 2050 if projections of disease growth hold up.

The needs of Alzheimer’s patients are complex and all-encompassing. These aren’t people who can be fixed by surgery. They don’t just need a nurse. These are folks who need everything. Someone has to feed them. Someone has to bathe them. Someone has to keep them from wandering away in the night.

The sound of a doorbell startles Gloria Bray from sleep. It’s around 5 a.m. She rushes downstairs, with Angel, a Yorkshire terrier no bigger than a shoebox, racing ahead. As Gloria flips on the living room light, Angel goes into full pit-bull mode, snarling and baring her tiny needle teeth at a young man standing on the porch.

“Mrs. Bray, Mr. Bray is outside walking around with hardly no clothes on,” the man says. Then Gloria sees her husband Oscar, once a proud man with impeccable grooming. A woman leads him by the hand. The woman was on her way to work when she saw Oscar and pulled over to help. Oscar is wearing Depends.

This is not an unusual story. Any family dealing with Alzheimer’s

has its tales: The battle over car keys. The refusal to bathe. The changed personalities. Sweet, calm people who grow angry and sometimes violent. Sharp-tongued people who mellow. Mothers who cannot remember their way home from the store. Fathers who cannot recall their children. Leave a note on the table that says, “Call me,” and you will be called every 10 minutes by someone who cannot remember she already did. A psychiatrist tells me his mother, now in her 90s, nurses fond memories of travels all over the world. In truth, she has hardly traveled at all.

Gloria Bray has trouble sleeping now, ear ever cocked for the sound of her husband’s cane on the floor. “You don’t know how his mind is working, what he might attempt. He may climb the fence,” she says. She’s been married 57 years to this sweet, gentle man who is now so changed, he has occasionally threatened her with his cane. On advice, she hid the knives in an upstairs bedroom.

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“I miss the companionship,” Gloria Bray says. “Just someone to talk to. We used to travel a lot. It was nothing for us to run down to Florida. I miss that. I’m just homebound now, really. I’m just homebound.”

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Oscar is no longer himself. “He curses now,” Gloria says. “He never did that. ‘Shut your damn mouth. Get the hell out of my face. Get out of my room.’” It hurts. Sure, he doesn’t know any better. Sure, it’s not the same Oscar she’s always known. But how do you not take these things personally? It’s one thing to know that your spouse is altered. It’s something else again to walk away from nearly six decades of feelings.

“I miss the companionship,” Gloria says. “Just someone to talk to. We used to travel a lot. It was nothing for us to run down to Florida. I miss that. I’m just homebound now, really. I’m just homebound.”

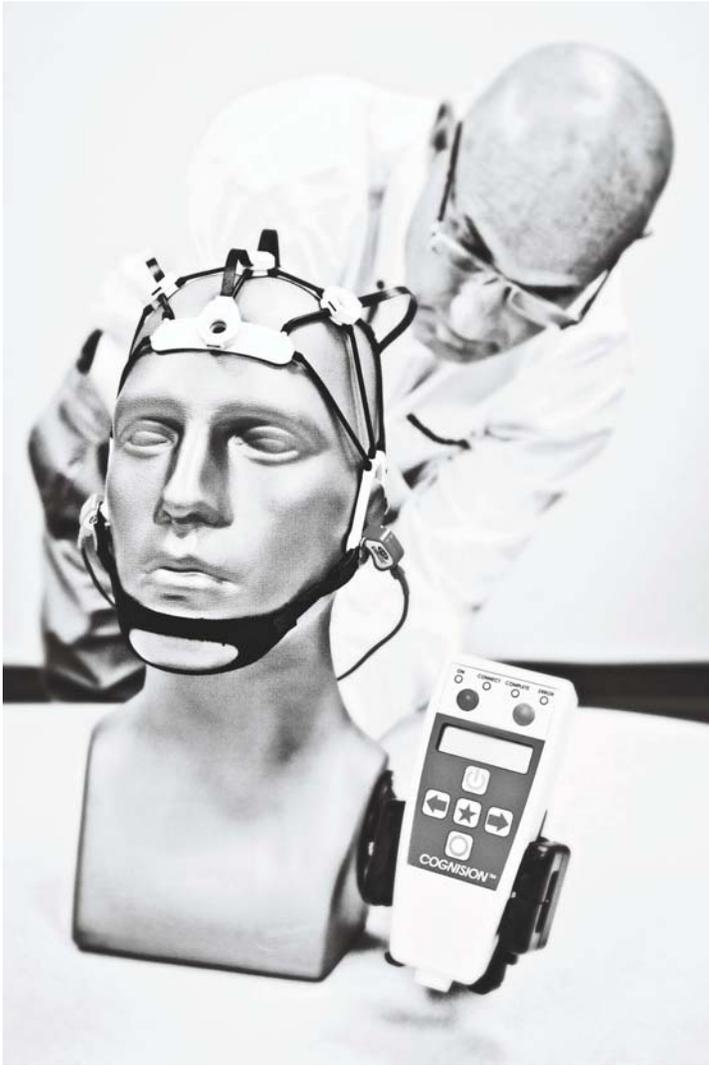
It’s a story that will only grow more common, says Teri Shirk, executive director of the Greater Kentucky/Southern Indiana Chapter of the Alzheimer’s Association. “Right now, we’re not prepared in Louisville, and we’re not prepared as a country. We do not have the in-home care support. We do not have the nursing-home beds. We don’t have the professional caregivers. We have to get prepared, or we better find a cure.”

It used to be cancer that scared the bejesus out of everyone. The Lord Voldemort of disease, people avoided the name: The C Word. It’s not that we’ve grown cozy with cancer, but it’s one of several killers that is just not as lethal as it was. In fact, among the 10 leading causes of death, Alzheimer’s, suicide and accident are the only ones with a higher rate of death in 2010 than in 2000. Since 2000, heart disease has fallen more than 30 percent, cancer mortality 31 percent, stroke 35 percent; and even diabetes has dropped a little, by 4 percent, according to the National Vital Statistics System. In that same time frame, Alzheimer’s deaths rose nearly 39 percent. It is now the No. 6 leading cause of mortality, and No. 5 among people older than 65.

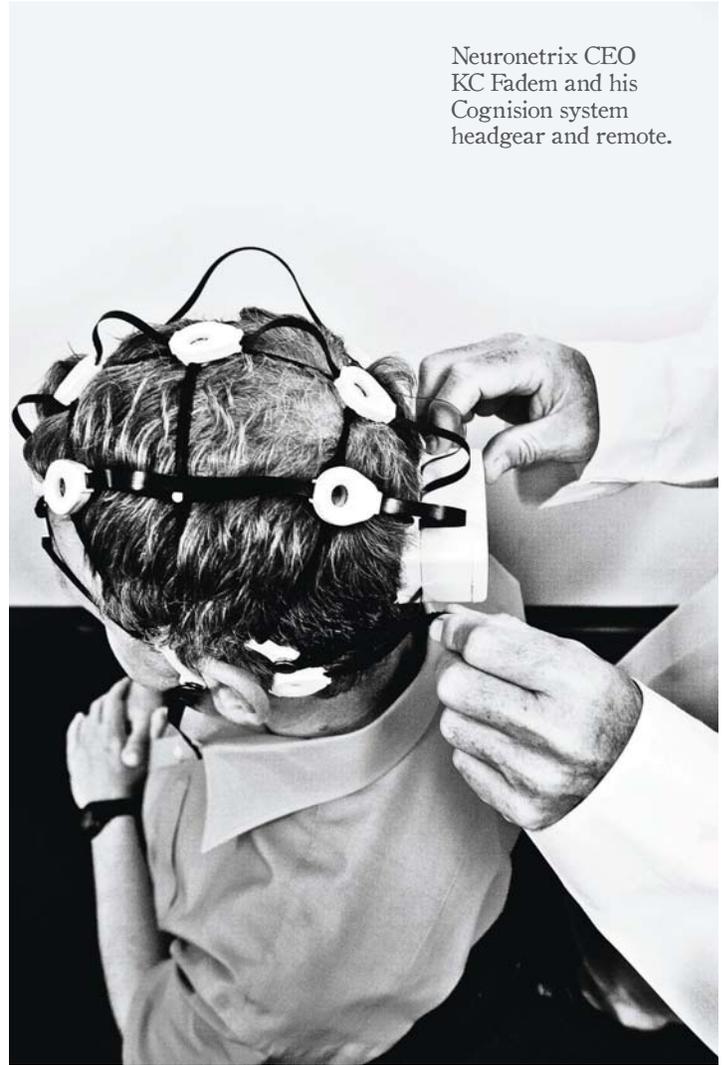
In the list of killers, Alzheimer’s is also the only disease with no treatment capable of changing its course. “You know if you’re diagnosed with diabetes, the doctor has things you can do,” Shirk says. “There’s absolutely nothing we know of that is going to prevent you from getting Alzheimer’s if you’re going to get it.”

But, Shirk says, “we know if we find a medication that can stave off the disease for just five years, it completely changes the cost trajectory.”

To date, there are only a handful of medications available to treat



Neuronetrix CEO  
KC Fadem and his  
Cognition system  
headgear and remote.



Alzheimer's disease, but they neither slow its progress nor reverse it. While they may temporarily delay the worsening of symptoms for six months to a year, even that record is only so-so, with fewer than half of all patients responding.

Adding to the complication of the disease, not everything diagnosed as Alzheimer's disease is truly Alzheimer's disease. So patients treated for Alzheimer's may not respond because they actually have something else. Or they may have several diseases. In fact, they're likely to. "It's a funny thing about cognitive impairment in aging," Nelson says. "The brain is by far the most complex organ of any in our body. It's geometrically and functionally complex; there is layer upon layer of complexity. But when people have impairment, they write it down to a single disease. That is a complete mistake. That is an error."

In fact, Nelson says, no more than 20 percent of those diagnosed with Alzheimer's disease have Alzheimer's disease alone. Unfortunately, these are diagnostic details available through only one mechanism: an autopsy.

Like everyone else who does brains for a living, Steven Scheff, associate director of Sanders-Brown, has a plastic brain on his desk, which he uses to punctuate his explanations, alternately pointing out its features and wiggling it around like a rubber chicken. Scheff is a pathologist, like Nelson. Both perform brain autopsies on UK volunteers. At the moment, some 700 people are on the list to donate their brains. When they die, a funeral home or a family member will call the "autopsy phone" that Scheff and Nelson take turns carrying.

When a body arrives at the lab, an autopsy technician runs a saw around the circumference of the skull — actually, the cut is toward the back of the head, where sailors wear their white caps. Already, the brain is undergoing rapid deterioration. When the heart stops pumping, things fall apart quickly, but nowhere faster than in the brain. Enzymes begin dismantling the machinery, degrading tissues, disintegrating cells. The sooner the brain is removed and preserved, the more it can tell researchers.

With the skull open, the brain is still not visible, but lies cloaked beneath a leathery jacket called the dura. Membranes extend from the dura to the inside of the skull, suspending the brain in a pool of cerebral spinal fluid that, in life, cushions the organ against its own weight and a rap on the head. The pathologist cuts through the attaching tissues and, tilting the head back, pulls the brain outward so he can reach in and sever its connection to the spinal column. Once that cord is broken, the brain is ready for inspection.

Sometimes, Scheff says, he knows even before the brain is out of the skull that disease has done its worst. The Alzheimer's brain is small, shrunken — instead of 1,300 grams (2.8 pounds), it may weigh 900, just short of two pounds. The once-snug arrangement of interlocking hills-and-valleys on the brain's surface is now a sloppy landslide, with much wider gullies and narrower ridges. In advanced Alzheimer's, a pair of little structures called hippocampi, where memories are knit together for storage, all but melt away.

But the deepest secrets are entwined in the cells, wrapped among the neurons.

In the pathology lab, Nelson starts pulling microscope slides from a yellow plastic box. There are more than 1,400 of such boxes in the UK brain bank, each box containing the samples of a single brain, revealing the details of its cellular anatomy on onionskins of tissue.

Nelson fits a slide onto a microscope and points out the neurofibrillary tangles — deep brown clumps of weeds inside cells made of a protein called tau. Another slide shows plaques, like black scabs, pushing the tissue out of the way, each scab making a Swiss cheese of the surrounding terrain. These two are Alzheimer's hallmarks, although their precise role in disease isn't entirely understood. Then Nelson pulls out another slide, this one showing signs of an entirely different disease, something called dementia with Lewy bodies, a cognitive ailment that includes some of the rigid movement that accompanies Parkinson's. Two diseases, one brain. That's the norm.

These are more than anonymous brains. They are connected to the years of testing that donor volunteers agree to. Once a year, Tom Conley and other prospective donors spend a half-day at Brown-Sanders for a mini physical and what Conley describes as "a grueling mental test."

"I'm competitive enough that I want to try to do my absolute best to get all these things correct," Conley says. "I also want to know how I compare to other people. But they won't tell me how I did, period." The results of this annual testing, combined with post-mortem exams, pushes knowledge forward, step by slow step. It's how researchers can correlate clinical judgment to biologic reality.

UK's is one of 30 National Institutes of Health-designated Alzheimer's brain banks and has been around since 1984. The Sanders in the name is actually Col. Harland Sanders. Brown is John Y. Brown Sr., whose son, former governor and former Kentucky Fried Chicken owner John Y. Brown Jr., donated money, through his foundation, toward construction of the Limestone Street building in 1972. Every day of the week, including holidays and weekends, the center sends an average of 7.7 brain samples to researchers all over the world. That's 14,000 samples of Kentucky brains every year.

Nelson came to UK seven years ago from the University of Pennsylvania for a courtesy interview and decided to stay when he saw what UK had. "I couldn't believe what has been built here," he says.

Not long after he arrived, laboratory staff member Wang-Xia Wang made a discovery that is leading to a potential Alzheimer's treatment. Volunteers are being recruited to enter a trial using the drug gemfibrozil, an FDA-approved cholesterol-lowering agent. Gemfibrozil acts on a bit of genetic material that plays doorstop to other genes. In the earliest stages of Alzheimer's, levels of this genetic material, called microRNA-107, fall. With microRNA-107 out of the picture, levels of the brain protein it used to block increase. This protein is believed to be responsible for higher levels of those nasty, scabby amyloid plaques.

Seventy-two people at risk of developing Alzheimer's disease will be recruited for this proof-of-concept study to determine if the drug has the Alzheimer's impact they're hoping for. "This particular drug targets the earliest stages of the disease," says Jicha, who will act as the principal investigator in the drug trial. If it's effective, he says, "we think it would confer natural protection." Because gemfibrozil already has FDA approval for another use, several barriers to its approval in Alzheimer's will be easier to leap if the drug works as hoped. "This could move through the drug-discovery pipeline at a dizzying rate," Jicha says.

It's one of several clinical trials ongoing at UK. Tom Conley is involved in a small proof-of-concept study testing a drug used in epilepsy and bipolar disorder known as valproic acid. This test in

people without Alzheimer's disease is only to determine drug safety. Ultimately, the drug could be tested as an Alzheimer's preventive agent.

For Conley, taking part in the trial, and doing whatever he can to help the center, is just doing his part. "I originally did it because I felt like, if (Nancy) has it, there is a reasonable chance our two girls could get it. We also have four grandchildren. If I can do something to help so that our children or grandchildren don't get it, then it's worth it."

Still, he's not worried about the future, and he's not worried about Nancy. "She's always been a very strong person. That's one of the things that attracted me to her. She just meets problems as they happen and deals with them." She was the owner of the store Bluegrass Frames, on Taylorsville Road near Jeffersonton. "We frame anything and anybody," she cracks. Now, one of her daughters runs the business.

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Nancy cannot remember recipes well enough to cook, Tom Conley says. As he talks, Nancy mouths the words "I don't want to cook!"

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Nancy, who says she feels as normal as she ever did, isn't scared. "I don't ever remember being afraid," she says. When she was a youngster, she contracted polio, and in fact, in 1947 became the second national March of Dimes poster child. She and her husband have a wall in their basement devoted to photographs of her year as poster child, including a framed version of the original poster showing little Nancy working a child-sized walker — something she never used in real life. She did, however, have pain, and still walks with a slight limp. "When you start out having polio, you learn what you have to do. I've never been afraid," she says.

For all his optimism, Tom can't help staying vigilant. There have been losses enough. Nancy cannot remember recipes well enough to cook, he says. As Tom talks, Nancy mouths the words "I don't *want* to cook!" When Tom says he does the cooking these days, she mimes wild applause.

"Every now and then, something will happen that will scare me," Tom admits. Returning home from an errand on a rare day when he didn't bring Nancy along, he saw her out getting some exercise in their neighborhood. She's 72 and looks great. She's slender, with short blond hair and blue eyes she uses like exclamation points.

"I stopped the truck and said, 'Hey, you want a ride?'" recalls Tom.

Nancy looked at him with a mixture of puzzlement and alarm and asked, "Who are you?"

"I said, 'Do you want a ride home?' And she said again, 'Who are you?'"

"I thought, one more time. I said, 'I'm your husband. Do you want a ride home?' And she said, 'Who are you?' And now I'm thinking, oh damn! I'm in trouble now. This is bad."

As Tom tells the story, Nancy is shifting in her seat, nearly wiggling. Her eyes open wide; she is signaling to me about something. She raises her hand to her mouth, as though whispering a secret so Tom cannot see it and mouths the words "I was lying."

"She was fooling around!" Tom says almost simultaneously. Nancy throws her head back and hoots. Tom, until that moment the most serious of serious men, cracks a smile. ■