THE DRIVE

IN HIS ZEAL TO UNDERSTAND LUNG DISEASE, PITT'S CHAIR OF MEDICINE HAS BEEN KNOWN TO EXPERIMENT ON HIMSELF  | BY CHUCK STARESINIC
The year that Steven Shapiro began his pulmonary fellowship at Washington University in St. Louis—1986—three of the five new fellows were MD/PHDs. Wash U, as it is informally known, is considered a biomedical research powerhouse, and these three new physician-scientists each had the aura of a first-round draft choice entering the big leagues. With their PhDs, they seemed to bring a lot to the table, including years of experience in the lab. Great research was expected of them in this competitive field of academic medicine.

Shapiro was not one of these three, however, which is not to say that he was a slacker.
Shapiro was studying human lung tissue the way that climatologists study tree rings or Antarctic ice cores.

infectious diseases to cardiology, plus an enormous amount of research. Traditionally, medicine is a medical school’s flagship department. Its stature helps to bolster that of all the other departments and of the school as a whole.

It’s a pleasant summer day when the elevator on the 12th floor opens to reveal Steven Shapiro lingering in the hall. He greets a few third-year medical students as they arrive. A few minutes later, Shapiro, the Jack D. Myers Professor and Chair of Pitt’s Department of Medicine since arriving from Harvard in 2006, presides over a conference-table gathering of eight of these students and one large plate of cookies.

In a pastel dress shirt and tie, Shapiro is broad-shouldered enough to occupy a significant amount of space beneath the basket. In a group like this—with medical students more than two decades his junior—he comes across as a sort of benevolent coach. He’s quick to laugh and wants the students to reciprocate. He’s not in a hurry. The students are wrapping up a semester-long clerkship in internal medicine, and they are here today for the last of a half-dozen or so grand rounds with the chair of medicine. Instead of presenting case studies, Shapiro uses this last session for his career talk. He wants to hear what the students see in their futures after what was, for most of them, their first sustained contact with real patients.

“I kind of like surgery, but the hours...” says one young woman.

“You’ve got to love to cut to do surgery,” says Shapiro.

“I want to have kids, I know,” says another. “But I don’t know how to do this—to get a job where I can pick up the kids after school. How old will I be when I can request that kind of time?”

Shapiro reassures her that, though there are challenges to having a family and a medical career, it’s getting easier all the time, even in some residency programs.

He says, “One of the little things we did this year when I took over is that we changed our Department of Medicine faculty meetings [from 5–6:30 p.m. to 4:30–5:30 p.m.] so that everyone can go and get kids from day care before six o’clock. I got e-mails and people thanking me—all women. Not one man. I also got grief—mostly from men in clinic, saying, ‘I can’t get out at 4:30. I’m working.’

“We’re also funding three grants for [faculty members] who are rising stars at a critical stage in their careers with unusual obligations. By and large, that is women with children.”

“I’m M D /PhD,” says one medical student. Then, a bit sheepishly, he admits, “I want to do the trifecta. I want to be in the lab, but I want to be clinically involved, too. And teach.”

Shapiro is galvanized by their enthusiasm. He talks about how their role models may change as they go through their training. They may find great clinical mentors in the hospital, as he did, then encounter terrific bench scientists in the lab.

Shapiro was captivated by the lab work. Now, he annually spends six to eight weeks doing clinical work in pulmonary medicine. He also regularly reviews cases with residents and interns.

Robert Senior, a professor of medicine at Wash U who was Shapiro’s primary mentor during his pulmonary fellowship, says that Shapiro’s eagerness for science showed immediately when he was a fellow. He developed a research project to try to understand the development of elastic fibers in the lung. (This elastic tissue is vital to the structure and function of the lung. When it breaks down, you get emphysema.) He obtained human lung tissue from people at all ages and developmental stages. He examined them for trace amounts of radioactive isotopes that were known to be in air pollution in specific years to determine when this elastic tissue had formed. He identified an amino acid in the lung that changes its structure over time, indicating its age.

This was totally novel work, says Senior. Shapiro was studying human lung tissue the way that climatologists study tree rings or Antarctic ice cores to date climatic changes. It was published in the prestigious Journal of Clinical Investigation, and it remains an important study of the topic to this day.

“Basically, what Steve showed was that the elastic fiber is extraordinarily stable in a normal lung,” says Senior. “To a large extent, what you have in midlife, or when you are even older, are the same fibers that you started out with.”

This is no esoteric question. In a normal lung, countless tiny air sacs clustered together at the end of your bronchial passages expand and contract with each breath. In emphysema, the thin walls between these little grape-like sacs break down as the elastic tissue degrades—the spaces enlarge and the lung loses elasticity.

At Wash U, Shapiro began a career-long interest in chronic obstructive pulmonary disease. COPD, as it is known, refers to a combination of diseases that cause difficulty with breathing—mainly emphysema, chronic bronchitis, and, in some cases, asthma. It is the fourth leading cause of death in the United States.

Approximately 90 percent of those who suffer from COPD are smokers or past smokers. In his zeal for answers, Shapiro actually became one of them for a few months.

He had what he thought was a great idea for an experiment. All that was required was a nonsmoker willing to become a smoker. If you have any sort of conscience, there’s only one person you can ask to do that. This was about 15 years ago, when he was a young, invigorated assistant professor at Wash U.
Institutional review boards weren't so restrictive back then, Shapiro says with a laugh.

Shapiro threaded a fiber-optic bronchoscope into his own lung. He maneuvered the flexible, camera-equipped scope through the mouth, delicately negotiated the larynx, then continued straight down the trachea and made a sharp turn into one nice, pink lung. Next, he used the attached syringe to spray a good 20 ounces of saline into his lung. Then, he suctioned it all out. The saline was now swarming with Shapiro's macrophages—millions of white blood cells that he believed would tell him interesting things about the progression of COPD.

His goal was to isolate the RNA from these macrophages, then to become a smoker, repeat the procedure, and see which genes were "switched on" when a nonsmoker became a smoker. This is an important question. Macrophages are the immune system's foot soldiers. They devour foreign matter, microorganisms, cellular debris, and abnormal or old cells. They are a key step in the body's targeted immune response because they present antigens to T cells, essentially showing the killer cells what the target looks like. Perhaps the toxins in cigarette smoke are responsible for activating genes in these macrophages that cause the destruction of lung tissue seen in COPD.

The experiment was kind of a bust, Shapiro says. Nowadays it might reveal more, because we've sequenced the entire human genome and could much more easily learn which genes are made active by smoking and what those genes do. He admits you could also probably learn just as much by comparing a large enough number of smokers and nonsmokers. But the experience did a few things for Shapiro: One, it got him to thinking very seriously about the macrophage and the limits of what he knew about genetics and molecular biology. And two, it gave him an enormous amount of sympathy—empathy, actually—for smokers who struggle to quit. He calls nicotine the most addictive substance known to man.

"Forget my morning coffee," says Shapiro of those three months before he quit. "I wanted my cigarette. I swear I had original thoughts about projects I'd been working on for a long time."

"He will sort of go where the good questions take him," says Senior, recalling Shapiro's self-experimentation, "and if it means he's the guinea pig, he'll do it. He has an incredible eagerness to learn things."

Senior's lab had been interested for some time in enzymes that these macrophages produce. Enzymes are powerful molecules that
break down specific types of proteins when they come into contact with them. Shapiro began to wonder whether a macrophage enzyme could be involved in the tissue damage that results in emphysema.

This was a bold question, because there already was a long-standing scientific explanation for emphysema.

Since the 1960s, doctors knew that patients with a condition called alpha-1 antitrypsin (AAT) deficiency often suffered terribly from emphysema, and they didn’t have to smoke much to get it. AAT was known to inhibit a destructive enzyme called neutrophil elastase, which cells called neutrophils produced. For decades, the obvious conclusion was that neutrophil elastase damaged lung tissue by breaking down the elastin. If you had enough AAT to inhibit the action of the enzyme, you probably wouldn’t get emphysema. People with AAT deficiency, however, were very susceptible to emphysema because they didn’t have the molecule that would inhibit it. This was dogma.

But something about it didn’t make sense to Shapiro.

There were actually rather few neutrophils in the lungs; macrophages were the most plentiful immune cells there. Could those few neutrophils produce enough neutrophil elastase to cause significant damage? Wasn’t it likely that macrophage enzymes were involved?

To test his theory, Shapiro did what no pulmonary scientist had ever done—he learned how to make a genetically altered mouse. This involved some of the most cutting-edge molecular biology techniques available at the time: tools that nobody anywhere in the field of pulmonology was using. Shapiro went into the lab of Tim Ley, a well-known oncologist at Wash U, to figure out how to tease apart the relevant genes.

“He saw the future,” says Senior. “He saw the importance of molecular biology, genetics, and the value of being able to manipulate genes to learn things. And nobody in the pulmonary division had those skills.”

McGarry Houghton, an M.D. and now a Pitt assistant professor of medicine, was a fellow in Shapiro’s lab at Wash U and has worked with him ever since. As Houghton tells it, Shapiro managed to get a bench space about the width of his shoulders in Ley’s lab, but he did a lot with it. (It’s a bit like occupying space beneath the basket but with less chance of taking an elbow to the nose.)

“He cloned [the gene for] this enzyme called macrophage elastase,” says Houghton. “He wasn’t even sure if it actually existed. He found it, he sequenced it, and he made a mouse that didn’t have it.”

Shapiro made a knockout mouse—one that couldn’t make the enzyme macrophage elastase. Then he devised an experiment that exposed this mouse to cigarette smoke—the knockout mouse didn’t get emphysema. Normal mice that were exposed to smoke did get emphysema. Clearly, macrophage elastase was important in the progression of emphysema.

In the pulmonary arena, says Senior, Shapiro “was the first person who put together the idea [to make] a gene-altered mouse, expose it to smoke, and see how it would affect lung injury.”

His discovery changed how people thought about lung injury, says Houghton: “That was in Science in 1997. The modern view is that it’s not one cell or one enzyme, because we know these cells work together, and these enzymes all work together.”

Shapiro says that he broke one of the cardinal rules of getting ahead in the business of academic medicine. His transgression: He was happy. He was completely content.

“Physician-scientists are working so hard to succeed,” he says, “they often forget what an honor it is to do academic medicine.”

Since 2001, he’d been the Parker B. Francis Professor of Medicine at Harvard University and chief of the pulmonary division at Brigham and Women’s Hospital, surrounded by terrific scientists and colleagues.

“His assembled a very good multidisciplinary group here, ranging from genetics to model animals to human studies,” says John Reilly, an associate professor of medicine at H avard who became the interim director of the pulmonary division when Shapiro left. He says the group was something special.

“In the type of group that Steve set up,” Reilly continues, “we could have our genetics guy here say, ‘Gee, we have this study that we’re just completing, and it makes it look like gene A is more common in patients with COPD, and nobody has ever reported that before.’ The question is, ‘Why would it lead to susceptibility to develop COPD?’ Steve can then take that and, in his mouse model, knock out that gene and see what it does in his emphysema model in mice. He can begin to do his experiments to define not only is the gene associated with the disease but why is it associated with the disease, which is the next step in developing therapies to treat the disease.”

Shapiro says that he interviewed for the job in Pittsburgh “to be polite,” which isn’t all that unusual. Good scientists get recruited all the time. And it’s tough to say, “No, thanks,” to a flattering invitation, especially when you have friends and colleagues at the institution in question, as Shapiro did in Pittsburgh.

“The people who answer ads are not the Steve Shapiros,” says David Perlmutter, who became friends with Shapiro (on and off the court) when they were both at Wash U.

Perlmutter is now Pitt’s Vira I. Heinz Professor and chair of pediatrics, as well as the chief physician and scientific director at Children’s Hospital of Pittsburgh of UPMC.

“I was thrilled he was going to look at [the job], but I knew that wouldn’t be enough. We were going to have to go get him.”

At first, Shapiro felt it wasn’t a good time for him to make a change. But the more he learned about Pittsburgh, the more he thought it was too good to pass up.

“I wouldn’t have taken a department chair job anywhere else,” he says. “I actually wouldn’t look at any others except for this one.” Right now, he says, there are very few academic medical centers that have it all going for them—strong scientists, dedicated teachers, excellent patient care, the physical infrastructure of top-notch hospitals, and profitability.

“The relationship between the hospital and the University is really special here,” he says. “You don’t see it anywhere else.”

Perlmutter calls this relationship “the cycle of life” in academic medicine, saying that Shapiro discovered “that the cycle of life is as good as it gets here. We’re expected to do a great job clinically, and we are expected to, in doing that, help the hospital make money to feed our education and research programs. And that cycle of life is administered here in a way that is really appealing to the department chairs. I don’t know of a place like it.”

For Shapiro, the emphasis on patient care is enormously gratifying:

“If a patient calls one of our clinics with a complaint, they get seen within three days, and that’s unheard of in medicine, even in private practice. But we know this is true because there is a ‘mystery shopper’ who calls all our clinics, documents the call, the time, and the wait.”

At Harvard, colleagues like Reilly and
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hapiro says that his lab has been more productive since downsizing and moving to Pittsburgh.

Remember the neutrophil? The immune cell famously and somewhat erroneously blamed for emphysema since the 1960s? Shapiro and Houghton are finding it can promote tumor growth in lung cancer. This is news. Researchers have long known that neutrophils could be found within a tumor, but what they were doing there has been misunderstood until now.

"We always thought that the macrophages and the neutrophils were your defenses to go and kill this tumor, which doesn't really turn out to be true," says Houghton. "You'd think they were going and trying to fight this thing, and some of the lymphocytes probably do. But in the model that we use, the neutrophil is actually being recruited by the tumor itself. The chemokines—the signals that tell the neutrophil to go to this place—are being released by the tumor."

The neutrophil, Houghton says, is adding things like neutrophil elastase to the tumor. But this enzyme isn't degrading proteins there, as scientists have long believed.

"A tumor cell with a little neutrophil elastase will grow at a more rapid rate," says Houghton.

Shapiro's team published on the tumor's neutrophil-recruiting abilities in a 2006 *Oncogene*. Now they are preparing to submit a manuscript describing the role of neutrophil elastase in promoting tumor progression.

"This is going to be big news," says Shapiro. "People were right all along, neutrophil elastase is very important. They just had the wrong disease. It is lung cancer not COPD."

"There's still a lot of misunderstanding of what the neutrophil does," says Houghton. "A lot of people think they are just kind of there. Nobody, I think, would imagine that they do such important things or that they impact tumor growth so drastically."

This kind of work is a perfect example of Shapiro's scientific instincts, says Houghton. "I just think he's kept his eyes open to what his data has shown him, and he's followed the data. He hasn't just ignored these interesting findings that might lead him in a different direction."

"It's really rare for a pulmonologist to study lung cancer. It's really been left to the oncology groups."

Another research project originated soon after Shapiro arrived in Pittsburgh, when he was asked to write a grant on asthma with Bruce Freeman, Pitt professor and chair of the Department of Pharmacology. His schedule was already jam-packed, and the molecular basis and pathophysiology of asthma were kind of outside of his area.

"I said, 'I'll do it, but I've got nothing,'" says Shapiro.

"That's one of the things that impressed me," says Freeman. "He was spending his full day learning about the people and the new aspects of his job—same with myself, because I'm a new chair—and we were getting up at three or four in the morning to do our research—"

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