

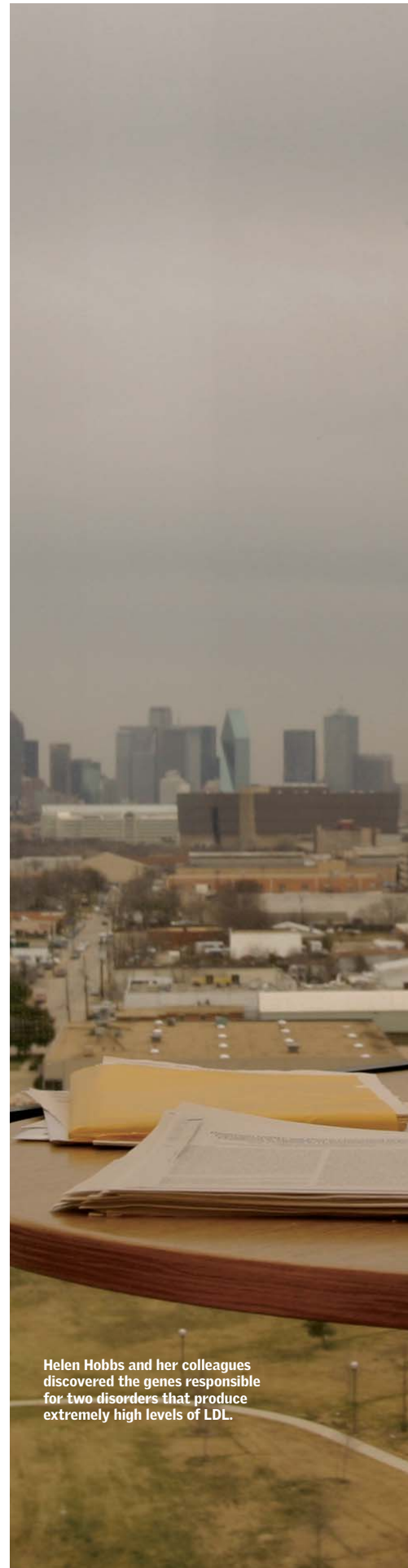
Ace of Hearts

Investigating the roots of heart disease, physician-scientist **Helen Hobbs** applies what she learns in the clinic to her successful research in the lab.

BY NANCY ROSS-FLANIGAN

Photographs by Danny Turner

NOBEL PRIZE LAUREATES Michael S. Brown and Joseph L. Goldstein still remember their reactions when they heard that Helen H. Hobbs was coming to work in their lab some 20 years ago. “We were very skeptical,” Brown recalls. ♥ It wasn’t that Hobbs, who was then wrapping up a residency in internal medicine, was inept, difficult, or dull-witted. On the contrary, she had already distinguished herself as a skilled chief resident in the pressure-cooker atmosphere of Dallas’s Parkland Hospital. “She became famous during that time for her ability to function in a crisis and treat very sick people, and she also had the ability to inspire and lead the others around her,” says Brown, a molecular geneticist at the University of Texas Southwestern Medical Center at Dallas (UT Southwestern). ♥ But laboratory research was an altogether different realm, and her mentors-to-be weren’t sure Hobbs was a good fit. “She didn’t even know what a pipette was!” recalls Goldstein, who is now an HHMI Trustee. Hobbs herself wasn’t convinced that a stint in the lab would work out, though the idea intrigued her. “I’d always been attracted to people who did science—I loved to hear their stories,” she says. “But I really had no experience in the lab at all.” Gregarious and outdoorsy, she also feared that the life of a research scientist would be too confining. “It seemed like such a singular, lonely pursuit that I didn’t think it would be appropriate for my personality.” ♥ But someone else—a very influential someone whose opinion was respected by Brown, Goldstein, and Hobbs alike—thought otherwise. Donald W. Seldin, then Hobbs’s boss as head of medicine at UT Southwestern, sat her down toward the end of her



Helen Hobbs and her colleagues discovered the genes responsible for two disorders that produce extremely high levels of LDL.



residency and asked about her plans. When she told him she intended to practice endocrinology, he offered the promising young physician a bit of advice. As Hobbs tells it, Seldin said “I think you’d like that for about five years, and then you’d wither on the vine. I think you should do research.” Hobbs didn’t argue. “I trusted his intuitions about me,” she says. “He’s a very bright and insightful man, and I knew that he knew all my strengths. But more important, he knew all my weaknesses, and he felt strongly that I should do this.” Brown and Goldstein, despite their doubts, didn’t argue with Seldin either when he asked them to take Hobbs on as a postdoctoral fellow.

Seldin’s instincts, it turned out, were right on the mark. Today, colleagues use words such as “brilliant,” “outstanding,” and “highly regarded” to describe HHMI investigator Hobbs and the work she continues to do at UT Southwestern. Focusing on the genetics of cholesterol metabolism, she and her research team have discovered the genes responsible for two disorders that produce extremely high levels of low-density lipoprotein (LDL)—the fat-and-protein complex that carries about 70 percent of circulating cholesterol. At present, they are studying the defective proteins behind these disorders. That knowledge, says Hobbs, could help reveal the details of how the body normally keeps cholesterol in check by regulating its uptake from food, shuttling it from the bloodstream into the liver, and excreting it into the bile.

In addition to overseeing her laboratory research groups, Hobbs runs the Dallas Heart Study. This intricate and innovative examination of risk factors and cardiovascular health in Dallas-area residents is aimed at tailoring treatment and prevention efforts for an ethnically diverse population (see sidebar).

EVEN DYNAMOS GET THE BLUES

IT’S A WHIRLWIND of a professional life, which she combines with a 23-year marriage and motherhood. (Hobbs’s husband, Dennis Stone, is vice president for technology development at UT Southwestern, where he is also a professor of internal medicine; the couple has two teenage sons.) But colleagues say that if anyone can handle it all with skill, finesse, and a touch of humor, Hobbs can. “Helen is total energy,” says HHMI investigator David J. Mangelsdorf, a biochemist at UT Southwestern. “She’s a dynamo.”

But even for a dynamo—maybe especially for a dynamo—the path to this point was no sure thing. Hobbs’s career was tough going at times, particularly during those early years in Brown and Goldstein’s lab when she struggled to make the shift from bedside to bench. “It was especially hard to change pace,” she recalls. “In medicine, everything happens very quickly. You make a diagnosis, and if it’s right, the patient gets well. If the diagnosis is wrong, the patient doesn’t get well and you have to

True Translational Research

Heading the population-based Dallas Heart Study—an examination of the biological and social foundations of the widening ethnic gap in cardiovascular disease—presents Helen Hobbs with a set of challenges different from those she encounters in her lab work. There are patient-recruitment and privacy issues, specific concerns of the ethnically and economically diverse population, and matters of managing an enormous database. But the payoffs are well worth the effort, says Hobbs. “It’s a different kind of science, but it complements the work that I do in the lab very well.”

The study, initiated in 1999 with funding from the Donald W. Reynolds Foundation, involves some 3,000 Dallas County residents—half of them African American—who have been extensively interviewed on their medical and family histories; health-care access, practices, and beliefs; environmental exposures; and other details related to socioeconomic status. During home visits, the subjects’ blood pressure, heart rate, and weight are recorded, and blood and urine samples are collected for analysis. They also come to the University of Texas Southwestern Medical Center for detailed physiological and imaging studies to assess

heart function, body fat distribution, signs of atherosclerosis, and other measures of cardiovascular health. Meanwhile, of course, their DNA sequences are recorded.

“Never has such a large and ethnically diverse population undergone such detailed phenotyping,” says Hobbs. “That’s what makes the study unique and very valuable in terms of trying to define the genetic underpinnings, along with the nongenetic components, of complex traits.” In particular, researchers can begin looking for DNA-sequence variations associated with specific cardiovascular risk factors.

While population-based studies can uncover only the associations between genetic and environmental factors and health—not the underlying mechanisms—they have some advantages over lab-based studies, says Hobbs. For one thing, “they’re large and they’re random, so they’re more representative of the population at large.” The ultimate goal—and challenge—is using the information to understand what contributes to premature heart disease and higher cardiovascular death rates among African Americans and to design education, prevention, and treatment strategies to address the problem.

Her focus in the Dallas Heart Study is to

probe ethnic differences in lipid and glucose metabolism and discover what these differences mean in terms of heart disease. For example, plasma levels of Lp(a), a lipoprotein known to contribute to the buildup of cholesterol on arterial walls, are 2- to 3-fold higher in African Americans than those in Caucasians and Asians. However, Hobbs has shown in the Dallas Heart Study that high plasma levels of Lp(a) are not associated with increased coronary atherosclerosis in African Americans, for reasons that remain unclear.

In addition, the prevalence of insulin resistance is higher in African Americans than in Caucasians, yet plasma levels of triglycerides—which are usually elevated in people with insulin resistance—are lower in African Americans. The researchers also have uncovered two intriguing differences in lipid metabolism between African American and Caucasian participants, and “we’re now trying to identify the genetic basis for these ethnic differences,” says Hobbs.

The heart study “is true translational research,” Hobbs says. “It’s clinical investigation tied to basic science, it brings people from different disciplines together, and it focuses on the community that we care for clinically.”

reassess.” That no-time-to-waste aspect perfectly suited the energetic Hobbs, who still bustles down corridors with the forward-leaning stride of a cross-country skier and often positions herself between two banks of elevators to make sure she catches the first one—only to get impatient and bound up the stairs instead.

But things moved much more slowly in the lab, especially for a rookie who was still learning the language and techniques. “I wasn’t a natural,” Hobbs admits. “Some people come into the lab—I see it with students—and they just have ‘the hands.’ They have an easy time concentrating and getting their experiments done without making mistakes. I had to learn that, and it was frustrating.”

What’s more, the persistent inquisitiveness that colleagues now appreciate in Hobbs wasn’t always seen as an asset—in fact, she had a reputation for being a pest in those early days. “When an experiment didn’t work, she would hunt down the one person who knew how to *make* it work, corner them, and make sure that they explained exactly how to do it properly,” says Brown. “Whenever Helen walked down the hall, everybody else would run the other way.”

No wonder Hobbs seemed glum when, a year or so into her lab training, she ran into a clinician she had worked with in her residency. He asked how things were going, and when she mumbled, “Well . . . OK,” he was taken aback.

“That doesn’t sound like the Helen Hobbs I used to know,” he said.

“Well, you know,” Hobbs confided, “every day that goes by, I feel like I’m becoming a worse clinician—because I get farther away from the clinical work—and I’m not even a very good scientist.”

But then, just as Hobbs was reaching her lowest point, something changed. “I started to have results,” she says, beaming. For the first time, she saw beyond the frustrations to the fun of doing science, and before long, recalls Brown, everyone else was tracking her down for technical advice.

SCIENTIFIC SLEUTHING

HOBBS’S EARLY WORK built on the research that earned Brown and Goldstein the 1985 Nobel Prize in Physiology or Medicine. For more than a decade before Hobbs joined their lab in the early 1980s, the two scientists had been studying familial hypercholesterolemia (FH), an inherited condition in which blood levels of LDL cholesterol are not only stratospheric but also resist any attempts at control through diet, medication, or lifestyle changes. People who carry two copies of the FH-causing gene can have LDL levels 6 to 10 times higher than normal and often die of heart attacks in childhood.

In the early 1970s, Brown and Goldstein had discovered that the disease stems from a defect in the LDL receptor—a protein on the surface



In addition to directing laboratory research, Hobbs runs the Dallas Heart Study, an innovative examination of cardiovascular health aimed at tailoring treatment for an ethnically diverse population.

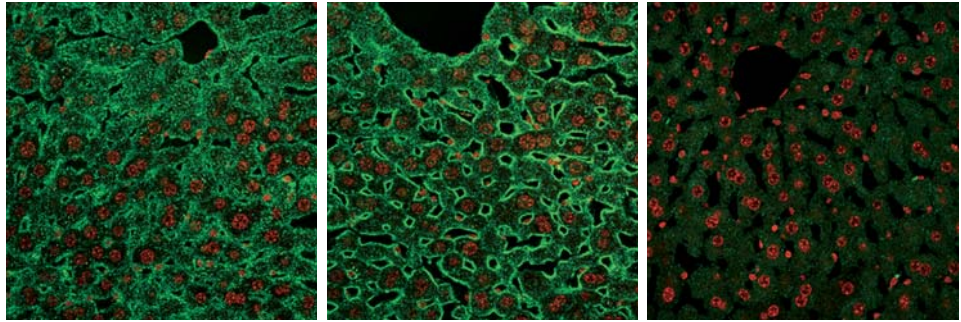
To keep her skills as a physician current, Helen Hobbs continues to see patients in the clinic.

of cells that snatches LDL cholesterol from the bloodstream and helps it into the cell. They went on to identify and clone the LDL-receptor gene, and when Hobbs arrived in their lab, they were trying to learn how mutations in the gene destroy the receptor’s normal function. One of Hobbs’s earliest successes was finding a mutation that alters the binding specificity of the LDL receptor—the first demonstration of such an effect.

Through the FH work, Hobbs was also introduced to population genetics and the scientific sleuthing it entails. FH can be a tricky subject for geneticists to study; although mutations in the FH gene are common, occurring at the rate of 1 in 500 people, many different versions—more than 900 at last count—can cause the disorder. So except in families, it’s hard to find groups of people with the same mutation. But certain populations—French Canadians, for instance—make the tracking job easier. “French Canadians are descended from between 5,000 and 7,000 immigrants who came from France to Quebec Province in the 1600s and 1700s and stayed very genetically isolated,” Hobbs explains. By studying samples collected from large numbers of French Canadian families with FH, she found that a whopping 60 percent of the patients had the particular mutation she was seeking, making it possible to track its route

through the lineage. “We were able to trace it back to the person who brought the mutation to the New World,” says Hobbs. “That really hooked me.”

Though she still interacts with Brown and Goldstein several times a week, Hobbs veered off in her own direction after a few years under their wings. Any early worries about losing her touch as a clinician or becoming a research recluse dissipated as she developed her own unique scientific style. Hobbs retains her clinical skills by seeing patients one afternoon a week. Most of these patients have unusually high or low levels of cholesterol or have had heart attacks in the absence of any known cardiovascular risk factors. With her outgoing personality, patients “love her and trust her,” observes HHMI postdoctoral fellow Christine K. Garcia, who works in Hobbs’s lab. And the extroverted nature that makes her patients smile turns out to be just as big an advan-



ARH is a protein that plays a critical role in the clearance of cholesterol from the blood. In mice lacking this protein, LDL receptors remain on the surface of liver cells and are thus unable to remove LDL, the major cholesterol-carrying lipoprotein, from the circulation. These liver tissue sections show the distribution of LDL receptor (shown in green) in (from left) normal mice, ARH-deficient mice (*Arh1*^{-/-}), and mice modified to express no LDL receptor (*Ldlr*^{-/-}). The red counterstain shows the nucleus.

Hobbs and her team are trying to identify and better understand proteins that may work to help ferry LDL cholesterol out of the blood and into cells.

tage in research, where a knack for assembling talented teams and motivating them to do their best pays off in high-quality results.

“I get a lot of pleasure out of running a laboratory and seeing people grow and develop as scientists,” says Hobbs. “It’s much like the pleasure I used to get in the wards.”

Striding into the lab, Hobbs rallies the troops with her exuberance. “What’re you up to?” she calls to a technician. “What’d you find out about the DNAs from Italy?” Later, in a lab meeting, she leans forward in her chair, chin in hands, scrutinizing data on a projection screen. “This is good! I’m just astounded!” she exclaims. The lab meetings, says Hobbs, “are where my sustenance comes.”

AREAS OF INQUIRY

LATELY, THOSE MEETINGS FOCUS on three main areas of inquiry. In the first, the group is following up on its discovery of two genes, *ABCG5* and *ABCG8*, that play crucial roles in maintaining the body’s proper levels of sterols, such as sitosterol (found in plant-based foods) and cholesterol—which in turn influence plasma LDL levels. The products of these genes regulate both the uptake of sterols from the diet and their excretion into the bile, and the researchers are trying to determine more precisely how they work.

A second project focuses on proteins involved in clearing cholesterol from the blood. In 2001, Hobbs’s team identified a gene that, when defective, causes a rare type of high-cholesterol disorder called autosomal recessive hypercholesterolemia (ARH). People with the disease have perfectly normal LDL receptors, but they are unable to clear LDL cholesterol from the bloodstream. The problem, it turns out, is that these patients lack an adaptor protein that likely tethers LDL receptors to the machinery that pulls them and their LDL-cholesterol cargo out of the blood and into liver cells. Hobbs and her team are trying to better understand this ARH protein’s normal role and to identify other proteins that may work with it to help ferry LDL cholesterol out of the blood and into cells.

In the third line of research, Garcia is following up on one of Hobbs’s early projects. While working with Brown and Goldstein, Hobbs studied a family in which some members with FH had high cholesterol levels as expected, while others with FH had surprisingly normal cholesterol levels. “It seemed that these people had also inherited a genetic modifier that normalized their cholesterol,” Garcia explains. So “the big question is, what gene is behind this modifier effect?” The original data, which Hobbs collected in 1988, were insufficient to answer it, but by studying additional family members, along with other families in which some members have unusually low LDL-cholesterol levels, Garcia and Hobbs hope to close in on the gene.

Also exciting is the prospect of using genes as biological crystal balls to predict future health—a quest that has so far proven elusive. “Despite what you read in the newspaper about genetic profiles, there really are very few examples where one can take a blood sample from a person, do a DNA test, and make any really competent prediction about their risks over the next 10 to 15 years,” says Goldstein. “Yet, heart disease is a condition that one should be able to do this for, because it boils down to things like LDL cholesterol being bad and HDL cholesterol being good. If one can understand all the genes that control these two lipoproteins, then one should be able to make more precise predictions. “If such questions are answerable,” he concludes, “Helen’s research is poised to answer them.”

Brown, the other early skeptic, couldn’t agree more with Goldstein’s assessment. “There seems to be no limit to what she can do,” he says. And not just do, but also accomplish with that infectious enthusiasm her colleagues now find so endearing. “With Helen,” says Brown, “there’s no such thing as a toe in the water.”