

A Silver Bullet for Blake

Unwilling to sit by while his youngest patients succumbed to Marfan syndrome, cardiologist Hal Dietz, MD '84, turned to bench science. His nearly two-decade quest in the lab has paid off big, bringing new hope to sufferers of Marfan—and a host of other devastating conditions.

By Elaine Freeman

REALLY LONG FINGERS. That's the first thing everyone in the delivery room noticed when Blake Althaus was born in November 2002. But if his mom, Anita, had dreams of Blake as a concert pianist, they quickly dissipated. "Is this curve in his spine normal?" she asked her pediatrician. It wasn't. Nor was the leaky heart valve. Nor the dislocated eye lenses. Nor the floppy muscle tone.

By the time Blake was two months old, Anita and Joe Althaus found themselves facing a geneticist who delivered chilling news: Blake had a particularly severe and rapidly progressive form of Marfan syndrome and would die soon. They'd be lucky if he reached age two.

Anita, a former social worker with the child protection division in Hennepin County, Minnesota, focused the skills she'd learned on the job on the survival of her son. "I'm good at networking," she boasts. And tenacious. Tearing through the Internet to learn about the strange condition that now controlled her life, she saw lists of people claimed as one of their own by the National Marfan Society—names ranging from Abraham Lincoln to Rent playwright Jonathan Larson. She came across stories about tall, lanky basketball players collapsing



Hal Dietz, MD '84, examines Blake Althaus, one of his Marfan patients.



KETH WELLS

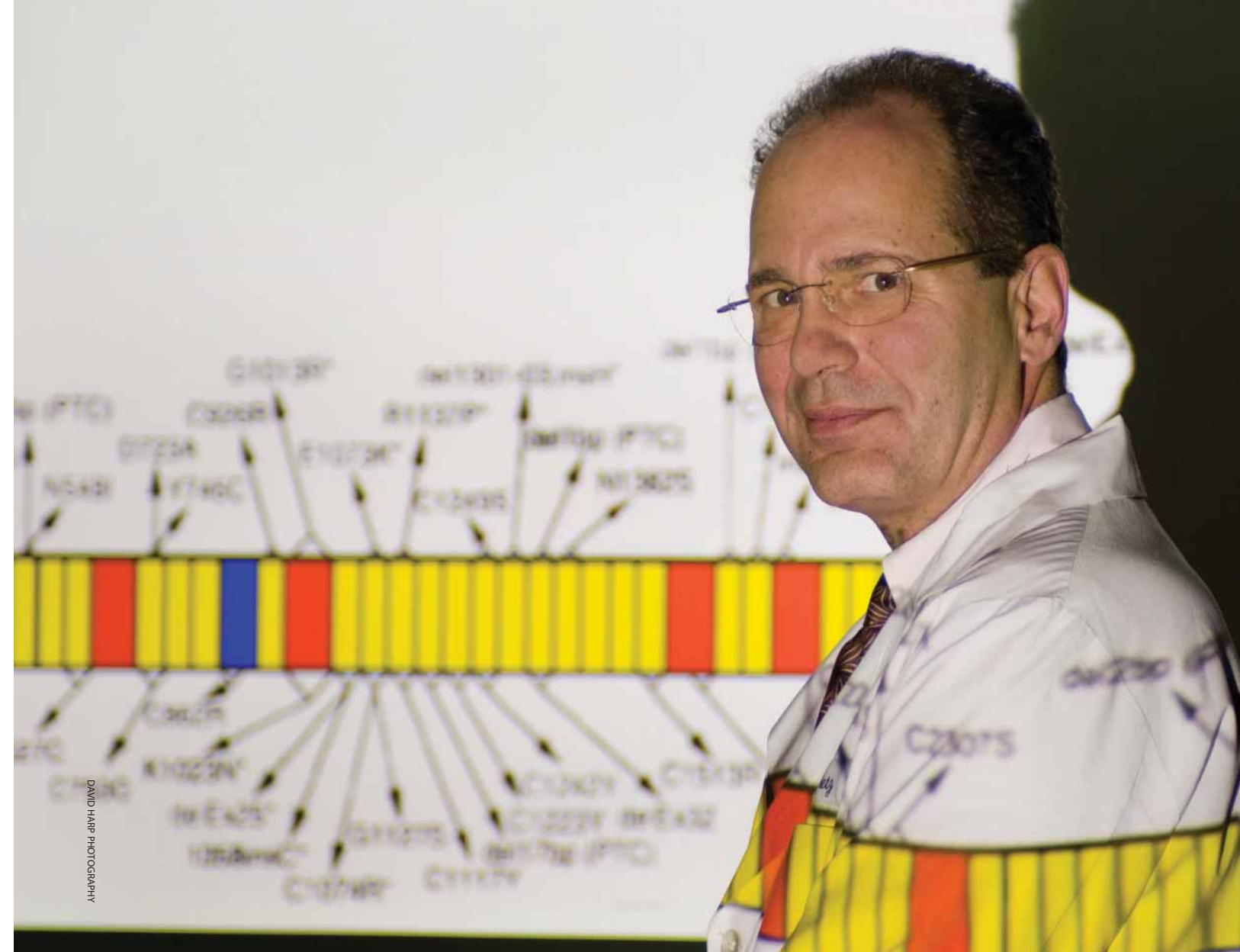
on the court and dying. Stories about families with a history of the condition. But there was no such history in her family or Joe's. What could any of these cases have to do with their infant son?

As she doggedly continued her search, Anita learned that in the athletes, a defect in the body's connective tissue—the protein glue that literally holds the body's cells together—slowly stretched and weakened the aorta, the major artery carrying blood from the heart, until it suddenly ruptured during exertion. In babies born with the rare, severe form of Marfan syndrome (MFS), the process is so accelerated they often die within a few years, their aorta ballooning for no apparent reason. The mutation in these cases is spontaneous, not inherited. These children don't live long enough to reproduce and launch a hereditary line. The geneticist wasn't exaggerating.

Desperately searching online for physicians who treat Marfan syndrome, Anita found many who care for adults with the problem. But when it came to children, the name that came up over and over again was Harry Dietz, MD '84.

She had no way of knowing that he, too, was on a quest that could mean life or death to Blake, nor that she had found him at exactly the right moment. After more than a decade of work, he was onto something that would turn the world of Marfan syndrome upside down.

Harry "Hal" Dietz graduated from Duke in 1980, from SUNY Upstate Medical University in 1984 (as valedictorian of his class), then easily made the jump to Johns Hopkins for four more years as an intern and resident in pediatrics and critical care medicine. For a bright young physician interested in a career in academic medicine,



DAVID HARF PHOTOGRAPHY

the next step was a postdoctoral fellowship. So in 1988, Dietz embarked on a fellowship in pediatric cardiology.

Once he made that decision, it was inevitable he would care for many people with Marfan syndrome.

While Marfan is a relatively rare disorder (1 in 5,000 worldwide), Johns Hopkins had been regarded as an international center of excellence for its diagnosis and treatment for half a century. University Professor Victor McKusick first published on MFS in 1955, in an article focusing on its cardiovascular aspects. In 1956, he made Marfan syndrome what he calls "the queen" of his landmark book, *Heritable Disorders of Connective Tissue*, describing the condition as solely due to weakness of a structural connective

tissue protein. That monograph essentially launched the field of medical genetics—and attracted a continuing flow of Marfan patients to Hopkins.

Connective tissue is found throughout the body. When it malfunctions, no part of the body is safe. With the benefit of more Marfan patient "material" than at most centers, McKusick's disciples attacked the plethora of problems confronting their patients.

Adapting procedures developed for other conditions, the team's surgeons, led by Vincent Gott, used Dacron grafts to bypass the ballooning aorta. Suddenly, the imminent death sentence hanging over many Marfan patients was gone. To replace stretched and leaky heart valves, the surgeons first

used mechanical valves and then learned to repair their patients' own valves. Physicians on the team developed expertise in treating problems particular to Marfan syndrome in the skeleton, eyes, nervous system, skin and lungs. Many people with MFS now live to age 70, but with frequent trips throughout their life to the "repair shop." Despite these successes, the disorder's genetic underpinnings remained unknown.

Enter Dietz.

Until that point, the young physician had focused on being a better clinician. "Research just wasn't how I focused my time," he recalls. "In clinical medicine, I felt a very personal connection to each person I cared for." In the late 1980s, however, a pediatric cardiologist specializing in Marfan

could offer little more than palliative care, referrals to good surgeons and a sympathetic ear. Frustrated, Dietz realized he could help his patients more by going into research.

"I can clearly remember the day in 1989 when I entered the office of Haig Kazazian, then director of the Center for Medical Genetics," recalls Dietz. "I asked if I could participate in a genetic study aimed at elucidating the cause of Marfan syndrome. Haig knew nothing about me, and I knew next to nothing about molecular genetics. Nevertheless, within hours Haig had assembled the team of individuals needed to promote my interest and nurture my development as a scientist."

"We were going through a golden age in genetics at Hopkins," recalls Kazazian, who would later head the Department of Genetics at the University of Pennsylvania. A decade earlier, in 1978, Hopkins' Dan Nathans and Ham Smith had won the Nobel Prize for discovering restriction enzymes, the biochemical scissors that cut DNA at specific sequences so it could be analyzed. As a result, says Kazazian, "in human genetics, we had lots of different projects and great people all thinking about basic mechanisms and opening entirely new fields. Hal was so sharp he sought advice from many people."

Dietz went to work in the lab of medical geneticist Clair Francomano, who quickly recognized that he has "absolutely golden hands in the lab."

Working 22-hour days, the newcomer to bench science made breathtaking strides, publishing his first two papers within two years. They were blockbusters. In one, Dietz mapped Marfan to a specific chromosome, chromosome 15. In the second, he identified mutations in the gene for fibrillin-1, a connective tissue protein, as diagnostic of Marfan syndrome. He had found the Marfan gene!

"Not a bad start for a new investigator," says McKusick drily.

Dietz still recalls in vivid detail that

"Eureka moment" in the darkroom when he found the gene. "It was 12 o'clock at night. I was feeling tired and lonely. Then suddenly there's this moment of insight, this precious feeling that no one else in history knew that piece of information that you know at that moment. That makes all the rest worthwhile—and there's a lot of 'all the rest.'"

Each time they returned to Hopkins, Joe asked Dietz, "What's going on with that miracle drug you're working on?" Twice the response was, "It's not ready yet."

Once the euphoria had passed, however, his mood changed. "It was a time of great pessimism," says Dietz, "because we still didn't know how to improve connective tissue throughout the body. How could you give a person something that's missing in every tissue? It was like a house built with a rotten frame. You can't imagine how to make the house better without tearing it down and starting over."

While connective tissue fell out of favor as an area of focus for most scientists, Dietz continued to plug away in the lab, making mouse models of Marfan and identifying mutations. Finally, in 2000 came what he calls "an even finer moment" than discovery of the gene. "I walked into a patient's room, saw his long fingers and thought, 'This just doesn't make sense.' Why should weakness of the tissues lead to overgrowth of the bone? You couldn't explain those fingers just with weakness of the tissues."

Obviously this wasn't the first time Dietz had observed long, spidery fingers in his patients. But it was what he terms "an epiphany moment." If the defect in the fibrillin-1 gene couldn't explain all of his patients' symptoms, then there had to be a second pathway, completely unanticipated, that was altered in the biological sequence leading to Marfan syndrome. As a wise man once noted, "Discovery consists in seeing what everyone else has seen and thinking what no one else has thought."

"Hal has more good ideas in a day than most people have in a year," says Hopkins pediatric geneticist Ada Hamosh, who also happens to be Dietz's wife. "Because he's not formally educated in science, he's not burdened by dogma. He's able to have any outrageous thought he wants. And like a dog with a bone, he won't let go 'til he has the answer."

In this case, Dietz's unique blend of inspiration and dogged persistence led to a growth factor dubbed TGF-beta as the mysterious pathway.

Transforming growth factor-beta is a family of signaling molecules that tell cells when to divide, where to migrate, what proteins to make—and when to die. Usually this occurs in an orderly, appropriate fashion. But triggered by a genetic defect, TGF- β may give totally different directions to different cells—all resulting in inappropriate behavior.

Dietz became suspicious when he realized that the structure of a TGF- β regulatory protein resembled fibrillin-1, the Marfan gene—and that TGF- β regulatory proteins bind to fib-1. If a mutation in the fib-1 gene causes a fibrillin-1 deficiency, he hypothesized, it also might unleash too much TGF- β activity, triggering a whole cascade of inappropriate behavior.

In the lungs of patients with Marfan, TGF- β might tell cells to die inappropriately, preventing division into alveoli, the small air-



Unburdened by scientific dogma, Dietz can see things others don't.

filled sacs necessary for normal breathing.

In the aorta, it might tell cells to make enzymes to break down tissues.

In muscles, it might suppress the ability of stem cells to regenerate muscle. In bones, it might tell cells to divide inappropriately. Too many cells, and abnormal tissue might form—such as the overgrowth of bone in the long fingers.

Block the TGF- β pathway and cell behavior should return to normal.

To prove his hypothesis, Dietz and his Hopkins lab team—which by 2003 had grown to 16 scientists—injecting an antibody to TGF- β into mice they had bred to serve as a model of Marfan. And then they waited. If they were correct, within two weeks they should see impact on the lung.

When it was time to sacrifice the first mouse, a general sense of excitement filled the lab. People paused in their own work and clustered around the microscope to view slides containing slices of its lung.

When Dietz entered the lab, removed his glasses and peered through the scope, there was a sudden silence. He smiles broadly when he recalls what he saw: normalized lungs with clusters of small alveoli. Proof of principle! TGF- β was an idea with traction.

But they'd have to wait six long months to observe any impact on the aorta—and as long as 15 months to see whether blocking TGF- β blocked its negative impact on muscle regeneration.

That's where things stood when Anita Althaus called Dietz' office early in 2003. Told that his next available appointment was in three months, she burst into tears, and cried, "But my baby's dying, and he's only 2 months old!"

Dietz's assistant calmed Anita down and asked how soon she could arrange to travel to Baltimore. A few weeks later, Anita, Joe—and Blake—had their first meeting with Hal Dietz. "Both Joe and I instantly loved him," says Anita. "Unlike the geneticist back home, he assured us 'Blake's not going to die of Marfan syndrome.'"

Anita's next question: "What can we do for Blake today?"

What was available were a number of palliative procedures, so Dietz arranged for consultations with a genetic ophthalmologist and an orthopedic surgeon. But while Anita focused on helping her son here and now, she says, "Joe looked to the future. He asked, 'What new things are coming along?'"

Dietz's response held out a glimmer of

hope. Something new was on the horizon, something that might halt Blake's progressively severe symptoms.

Six months later and six months after that, the entire Althaus family returned to Baltimore. Anita's mom stayed in the hotel room with Blake's older sister, Jenna, and later also with the new baby of the family, Chase, while Anita, Joe and Blake saw Dietz and their team of Hopkins physicians. "For a family of four or five to fly out every six months is a financial burden," Anita admits, "but we would beg, borrow and steal to get to Johns Hopkins."

Nor did she hesitate to battle insurance companies that didn't want to pay for Blake to go there. "I told them that if I have to, I'll go to every news channel in Minneapolis."

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Back in the lab, at the appointed time in maturation of the Marfan mice they'd injected, Dietz and his team had been analyzing each new set of tissues. After the lungs, exults Dietz, "I recognized the mice had normalized heart valves. And then that the aortic aneurysm was completely blocked. This showed that TGF- β was not just a player, but the major player!"

Proving that TGF- β was what Dietz calls "the culprit that caused cells to behave badly" gave him immediate insight regarding a possible treatment for patients: Inhibit TGF- β and block the destructive process. Frequent injection of a TGF- β antibody was not a practical solution, however. He needed a safe medication that would have the same effect. For humans, not mice, the answer was still "not ready yet."

Then, amazingly, a literature search revealed that in animal models of a few rare conditions, a drug called losartan inhibited TGF- β . Losartan was hardly a new drug. Marketed by Merck for several decades as Cozaar, it was best known for lowering blood pressure by blocking an angiotensin receptor. And it was safe. It was even approved by the FDA for treating high blood pressure in children as young as 6.

To validate his theory of the link between the signaling molecule and Marfan—and to prove that losartan could break that link—Dietz and his team designed a classic comparative study in Marfan mice and focused their attention on the aorta.

When the mice were seven weeks old, and their aortas already had begun to change, the researchers began adding losartan to the drinking water for 15 of them. Fifteen more were injected with placebos. A final 15 received a beta-blocker, propranolol (a drug that's been a standard of care for Marfan patients; by lowering blood pressure, it reduces stress on the artery, even though it does nothing to correct the underlying defect).

Six months later came the moment of truth. When Dietz checked tissue from each group of mice, he found that those in the losartan group appeared indistinguishable from normal mice. Their aortas no longer showed any damage. None. The earlier damage literally had disappeared, while the aortic damage in the mice receiving placebos or beta-blockers had grown worse.

"It was truly a jaw-dropping moment," Dietz told *Science* magazine's reporter, throwing his usual reserve to the winds. "It was beyond anything I could have anticipated or hoped." Now he had proof a drug already approved by the FDA might hold the answer to the "rotten frame" ravaging the bodies of Marfan patients.

Meanwhile, Anita and Joe Althaus were panicking. Blake had an echocardiogram every three months, and each time the test

showed that the baby's aortic root—the spot where his main artery exited his heart—was dilating more and more. He would need heart surgery sooner rather than later. And because his body wasn't big enough for a graft that would take him through growth, he was destined to have subsequent surgery down the road to put in a bigger tube to accommodate his blood flow.

Finally, when Blake was almost two, Dietz gave the worried parents the news they were waiting to hear: He was ready to try his new drug on Blake—if they were ready.

Hal Dietz has a perfectly cool demeanor, yet admits that "anxiety" is his "connective tissue." He recalls long discussions with

Excitement in the Marfan community at losartan's potential to block symptoms is gut-based, personal, emotional. As the president of the foundation told a reporter, "This breakthrough is so full of promise that people have chills."

Anita and Joe about what was known, and not known, about losartan. "When Dr. Dietz finally said Blake could go on the medicine, he said we should go home and think about it," says Joe. "We said, 'We've been thinking about it for two years. We're ready!'"

Anita triumphantly recounts what happened next: "Our cardiologist was skeptical. He said, 'It's been on the market for 25 years; my mother's on it!' But at Blake's first check-up after starting on the medicine, for the first time there was no growth in the aortic root. Our cardiologist thought it was just a fluke. When there was no growth in the aortic root at the second check-up, he said, 'It still doesn't make me a believer.' Three months later, he said: 'I'm absolutely sold.'"

Losartan did more than stop Blake's aortic root growth. It also increased his

appetite. According to Anita, "He's gained some serious weight. Now he looks like a normal little boy who is tall and thin."

Photos of Blake taken before he started on losartan, then six months and a year later provide graphic proof that he didn't just put on weight, but gained muscle mass and strength. In the first shot, slumped in a chair, pale, blonde and blue-eyed Blake looks like Antoine de St. Exupéry's fragile Little Prince. By the second, his little muscles are bulging as he totes a heavy, water-filled bucket on the beach. By the third picture, he's mugging it up for the camera as a muscle man.

Losartan hasn't cured all of Blake's problems, however. The medicine has helped

some with the elasticity in his stretched tissues and floppy joints but not in time to prevent the twisted vertebrae from touching his spinal cord. Two complicated surgeries were required to correct that condition. Fortunately, they could take place close to home, at Gillette Children's Hospital in St. Paul, after consultations between pediatric orthopedic surgeons there and at Hopkins. With Blake's next surgery, two sets of rods will be inserted to keep his spine straight. They'll need to be adjusted every six months until he's 15 or older, when he'll be ready for a spinal fusion. To prevent scoliosis—curvature of the spine—until then he'll also need to wear a firm plastic brace that goes from under his arms to his hips.

Some maturation also is required before his vision is corrected. At first, Blake was



Anita and Blake Althaus, at home in Minnesota.

extremely near-sighted. Now his lenses are loose and floating, so he's both near and far-sighted. In any case, losartan should prevent the glaucoma, cataracts and retinal tears that used to plague those born with MFS. And one scientist in the Dietz lab now is looking specifically at the role of TGF- β in eye tissues.

Now four, Blake started preschool last year. His mother reports that he likes it a lot, despite his problems. He can't climb on the jungle gym, and because of poor vision from the dislocated lenses, needs help so he won't trip. His teachers watch him to try to prevent falls, says Anita, and "when he goes potty, he needs help getting his pants down because of the brace."

Anita explained Marfan syndrome to the parents of Blake's classmates, but she also told them "otherwise, Blake's just like any other kid. He likes to play cards, go to birthday parties and go fishing with his dad."

Highly verbal since he was one, Blake's also pretty good at standing up for himself. When kids ask him to wrestle, he says, "I can't because I have Marfan." When he's fed up with wearing the brace, he tells Anita, "A guy needs a day off." And sometimes she agrees. He knows why he's so tall, and when he sees someone else who seems exceptionally tall, asks, "Does he have Marfan?" Sometimes, says Anita, "we're thinking the same thing."

Not surprisingly in a family that's contended with the syndrome for almost five

years, Jenna, now 6, insisted for a long time that her doll had Marfan.

Blake Althaus was not alone in receiving "off-label" losartan. Dietz also prescribed the drug for 15 other young patients with rapidly expanding aortic roots. He has carefully monitored their progress and expects to publish a paper on this early clinical experience. The results to date: "Very clear evidence that losartan protects the aorta."

Off-label use is not good enough over the long run, however. To prove beyond a doubt that losartan should be the new standard of care, Dietz organized a true double-blind study with a co-principal investigator at Harvard and with the Pediatric Heart Network (seven medical centers brought together by the National Institutes of Health to study problems in children with heart disease). To enroll participants quickly, 10 other centers with large Marfan pediatric clinics are participating in the losartan trial, which launched early in 2007.

The study will follow 600 patients, ages six months to 25, over three years. Half will receive losartan and half atenolol. At three interim points during the study, scientists on its Data Monitoring Safety Board will look at results. If there is unequivocal evidence that losartan is better at stopping the aorta's growth, the trial will be cut short, and everyone will be started on the drug.

While the core trial is only studying the effect of losartan vs. atenolol on aortic aneurysm, efforts are under way to find funding for trials that can study losartan's possible effects on other body systems, including lungs, bones, muscles and eyes—in the same people who participate in the core trial. Thanks to an initial gift to the National Marfan Foundation, studies of muscle and of biomechanical aspects of the aorta are proceeding.

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So will children like Blake now be cured and grow up free from risk of early death?

“We haven’t eliminated the disease,” says Dietz, who today directs the efforts of 20 researchers through Hopkins’ William S. Smilow Center for Marfan Syndrome Research. He notes that the same question probably came to mind when aortic surgery for Marfan was first developed. “It allowed most people to live a normal life span simply by changing the natural history of the disease, but it hadn’t eliminated it,” he says, noting that some patients require additional surgery to correct dissection of the descending aorta. And some die of an aneurysm, though at an older age than they would have previously.

“It’s possible,” he says, “that losartan won’t eliminate Marfan syndrome but will get us to that next step in changing the natural history of the disease.”

Dietz is less sanguine, however, about losartan’s ability to prevent sudden death from a ruptured aorta. “In retrospect, most of those who died suddenly had all the markers and should have been recognized. You can’t wait until someone dies in the family to start thinking ‘Could it be Marfan syndrome?’

Primary care practitioners must recognize this condition in order to diagnose and treat it.”

His advice to these doctors is clear-cut: “Pay attention to certain patterns of skeletal abnormality. Watch for individuals who are not just tall but extremely tall for their family, or have legs much too long for their body. Look for chest wall deformity and curvature of the spine. Most often it’s the skeleton that tips people off,” he explains. “Once you know what to look for, it will become obvious that certain people need further evaluation.”

At the beach, Dietz’s 10-year-old daughter, Nina, like Blake and Jenna Althaus, has developed a clinician’s eye for picking out people with Marfan and pointing them out to her father. Hal Dietz admits that sometimes he can’t resist going up to perfect strangers on the beach to tell them, “I treat people who look like you and have a treatable condition.” He adds, “I emphasize the ‘treatable’ and suggest they see their doctor. Usually people are receptive. Sometimes they’re hostile and say, ‘I know. I’m on vacation to forget my troubles. Leave me alone!’”

Blake Althaus probably will need to stay on losartan for life. “Each morning,” says his mom, “I lay out his medicine with a cup of milk, and he takes his own meds. He’s an old soul. It’s hard to believe he’s

just 4. He’s been through a lot and takes it like a champ.”

Living on a cul-de-sac with 17 children, the Althaus offspring are outside from sunup until sundown every summer day. Playing in the backyard sandbox, catching tadpoles in the neighborhood brook, collecting rocks, Blake is one of the gang—but with an adult always hovering nearby to catch him if he trips.

From the kitchen, Anita can watch Blake riding his Big Wheel outside on the patio, the limits of his permitted bike universe. Trying to cut the apron strings, Blake tells her, “I’m fine. Just let me do this!”

Blake’s fifth birthday is approaching in November. His aortic root hasn’t grown in three years. At birth, it was the size of a 45-pound child’s. “Now it’s more normal, not so much of a worry,” says Anita. “We don’t think about the heart all the time. I just realized, ‘Oh my gosh, it’s been four months since we had an echocardiogram.’”

The leak in Blake’s heart valve also is resolving, Anita reports. “It went from moderate to mild to now it’s barely there.” As far as she’s concerned, “Blake’s silver bullet really is a miracle drug.”

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Beyond Marfan: Losartan’s Promise

Discovering that TGF- β is the critical pathway in Marfan could lead to breakthroughs in the treatment of other conditions. The picture that’s emerging, says Hal Dietz, “is that many forms of vascular disease,” including aortic aneurysms, “are caused by too much TGF- β signaling.”

Dietz and his protégés are particularly excited about losartan’s potential to treat muscular dystrophy (MD). In Duchenne muscular dystrophy, the most common form, as in Marfan syndrome, muscle weakness is due to the inability of stem cells in the muscle

to repair damaged muscle cells. TGF- β turns out to be the culprit in blocking muscle cells’ normal regenerative ability. The Dietz team proved this in a mouse model, then used losartan to block the TGF- β signal, clearly correcting the malfunction. They published their results in January 2007 in *Nature Medicine*.

While losartan doesn’t prevent muscle destruction, it facilitates regeneration of new muscle cells. For MD patients, this could slow progression of the disease and improve muscle performance and breathing—without pernicious steroids. To test this possibility, Ronald

Cohn—who now has funding to establish his own lab—is planning a clinical trial with the Muscular Dystrophy Association.

Dietz’s collaborators also are pursuing other leads for losartan. One postdoc is looking at a geriatric population: What’s the difference in body mass of individuals who took losartan for hypertension vs. those prescribed a beta blocker? Another is looking at rare genetic models of premature aging. Still another is focusing on muscle weakness in patients on chemotherapy. Losartan might have a role there, too.