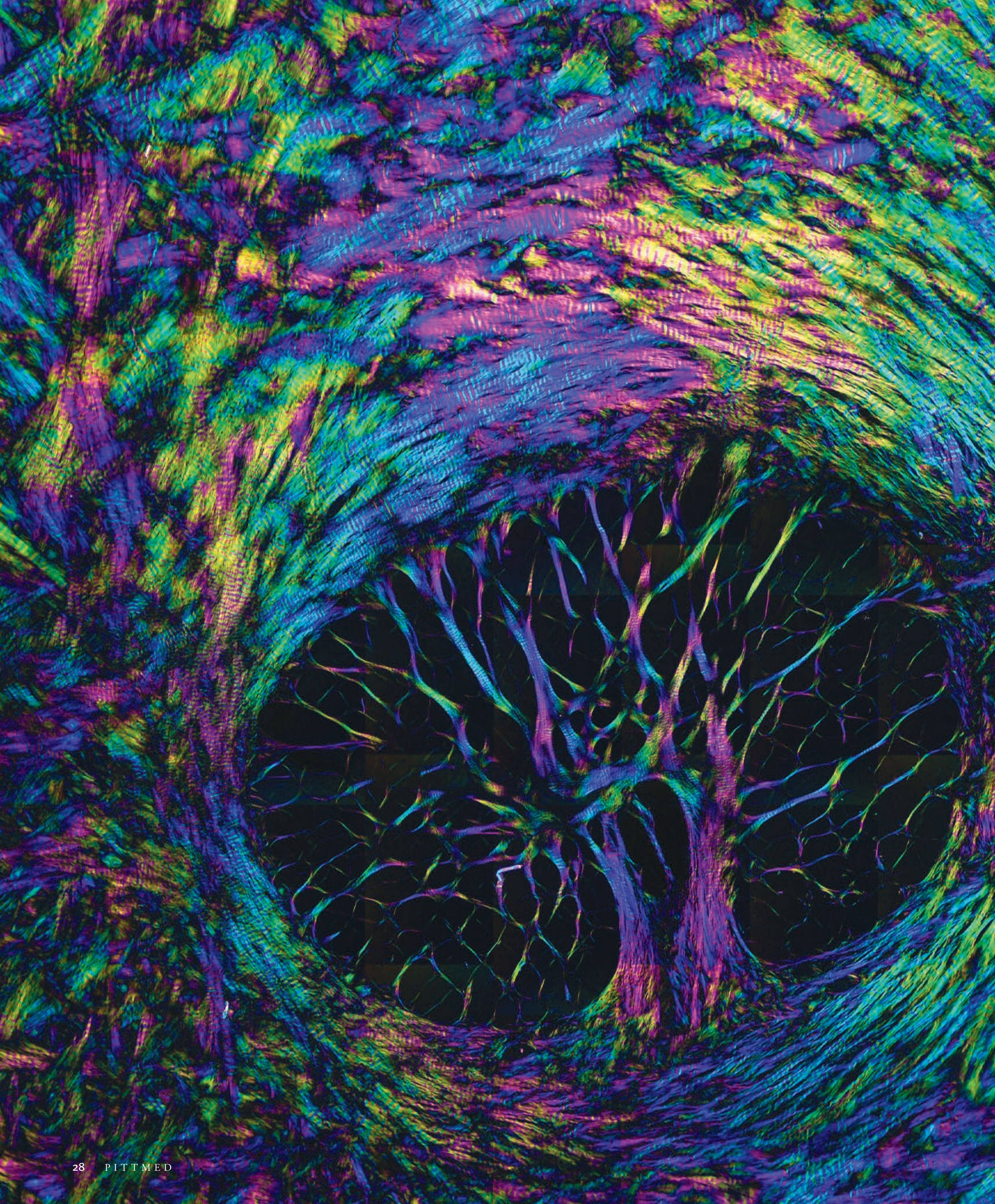
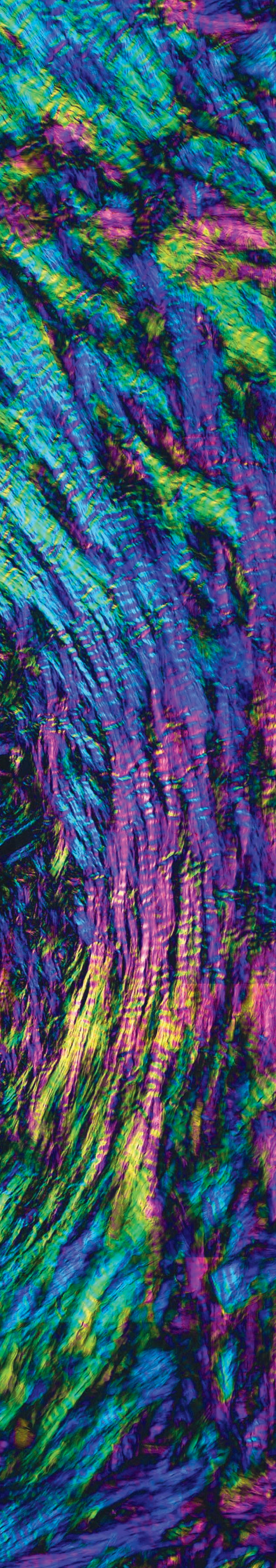




THE LANDSCAPE OF THE EYE IS EVER-CHANGING

BY ELAINE VITONE

THE FOREST, THE TREES, AND THE LEAVES

When Ian Sigal was a PhD student researching glaucoma—a group of disorders marked by damage to the optic nerve—he and his advisor homed in on those dying nerve fibers for their studies. But soon, they realized they couldn't understand what was going on there without also checking in on the optic nerve's nearby neighbors. So they widened their scope a tad.

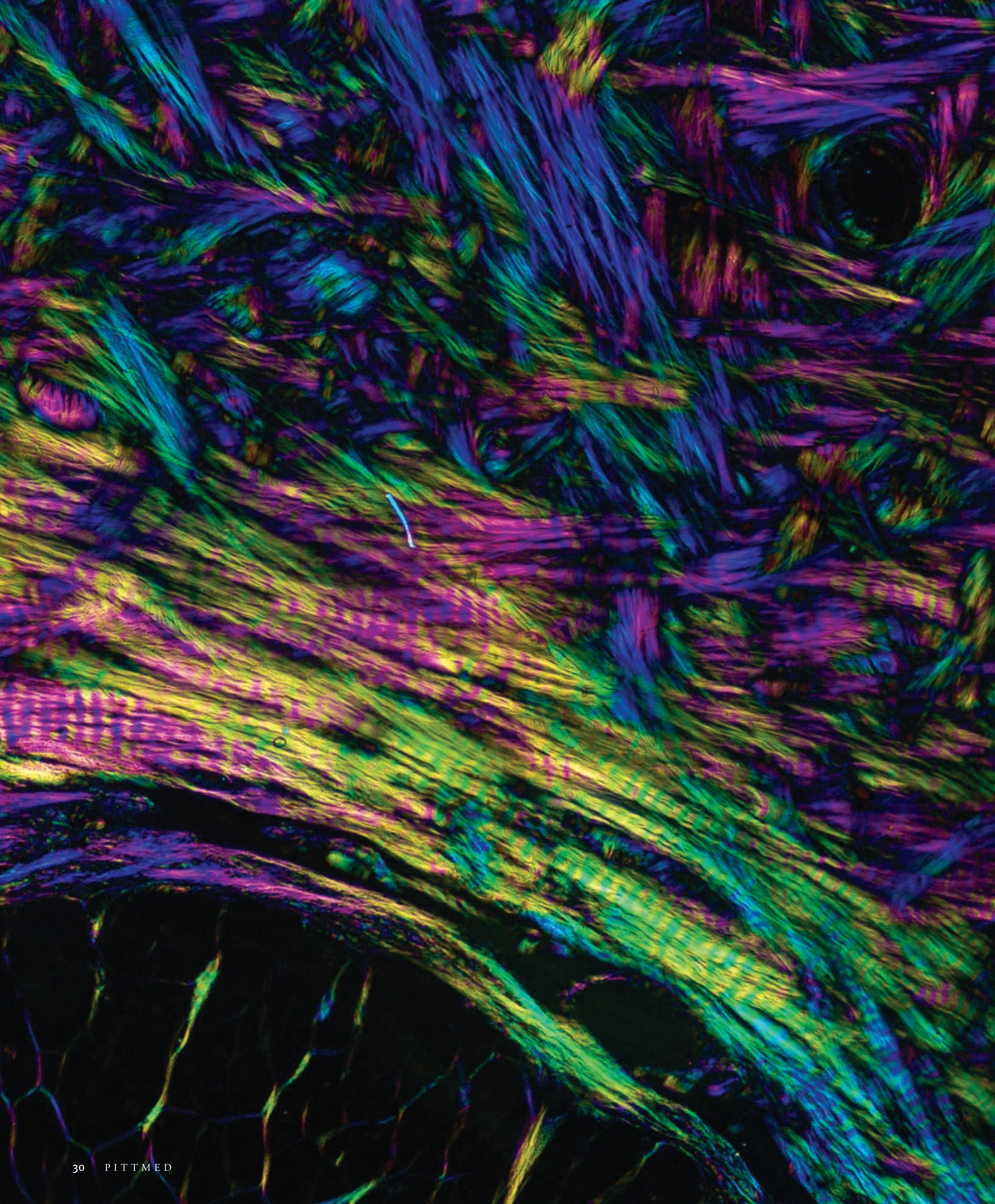
"Then we found, of course, that no, that's not enough," Sigal says. You have to look around that area, then you have to look around *that*. So they kept expanding their scope.

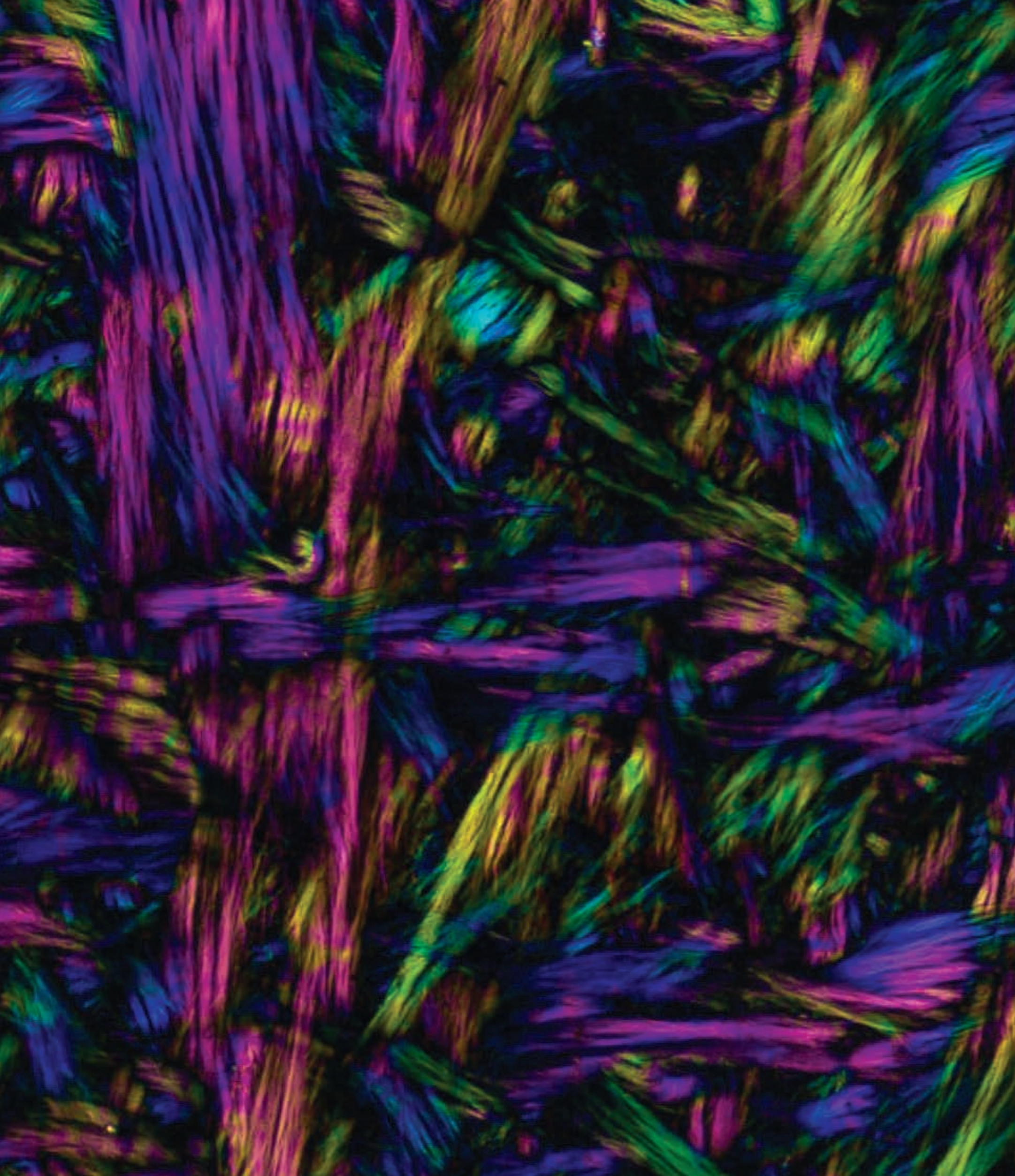
In time, he learned that changes within the eye don't happen in a vacuum. Hence, Sigal, founding director of the Laboratory of Ocular Biomechanics in the University of Pittsburgh Department of Ophthalmology, studies the whole enchilada—the dynamics of the complex organ in its entirety.

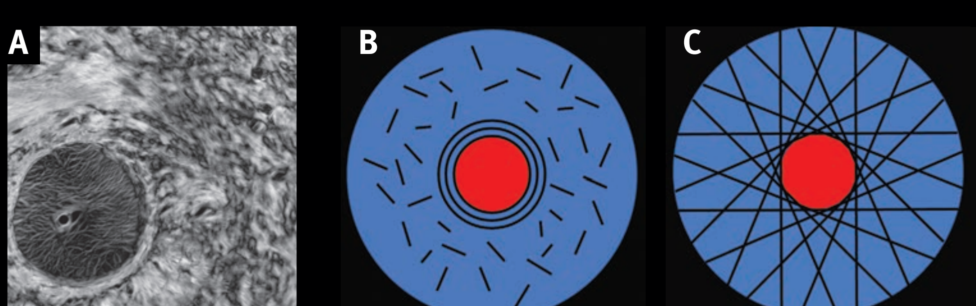
Traditional imaging methods used to make this difficult, he says. Imaging the delicate tissues in the back of the eye was slow going and very uncomfortable for patients. But in the last couple of decades, a 3-D imaging technology called optical coherence tomography, co-invented by Pitt's former ophthalmology chair Joel Schuman, "changed everything in ophthalmology," Sigal says. Or at least in how ophthalmology sees the eye, so to speak.

The eye is a biomechanical wonder. A delicate balance of forces is at work every time you focus on a word or follow a line of text across a page. Fluctuating pressure pounds on the back of the eye, where the optic nerve begins; and in some people, those nerve fibers deteriorate, causing vision loss (glaucoma). Yet a certain amount of pressure is necessary for the organ to maintain its shape and function. The eye is like a soccer ball, says Ian Sigal. "At some point, if it's too deflated, it just doesn't work. You can't play."

IMAGES COURTESY IAN SIGAL/LABORATORY OF OCULAR BIOMECHANICS, EXCEPT FOR PAGE 31



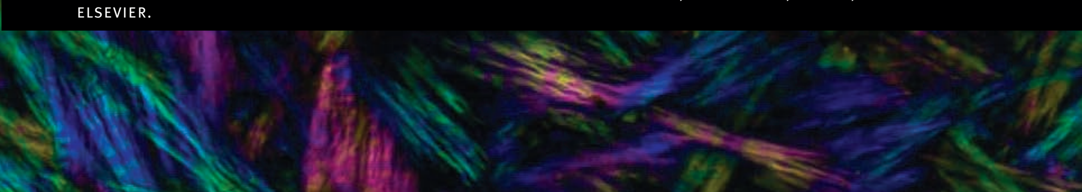




There's a lot going on in the back of the eye, at the portal where it plugs into the rest of your nervous system. It's essentially a hole, right in the middle of a pressure-burdened structure called the sclera. "And what did nature end up putting in that hole?" asks Sigal. "The axons—the most fragile part of the nerve fibers. Sounds crazy! That's one of the reasons we study this."

Conventional imaging (A) suggested a model wherein the hole is wrapped in rings of reinforcing collagen (B). But, as it turns out, those circular fibers were an optical illusion. Sigal's team designed a new technology, a modified form of polarized light microscopy, which revealed multitudes of crisscrossing lines (opposite page). In their new model, the fibers are arranged kind of like a basket weave (C).

The team learned there are lots of reasons why nature would choose this arrangement. A ring would mean one region determines the fate of the whole thing; but a weave spreads the burden more broadly. In Sigal's computational models, "the stresses were lower, the deformations were lower, it's much more robust" in the weave, he says. When damage befell the area around this all-important portal, the whole system shifted to relieve it. And "sometimes the biggest problems were actually far away from this region."



Previously, imaging in this field was limited to either low-res views of the big picture or very hi-res views of cells and their components, and nothing in between. To make that sought-after middle ground possible, Sigal's lab has employed a technology of its own design—a variation of what's known as polarized light microscopy (PLM)—yielding new insights into the organ's inner workings.

On a recent afternoon, at his computer in the Eye and Ear Institute, he clicks through images of animal eye interiors, brilliantly rendered with stunning detail, like postcards from a dense, day-glow thicket.

"Now we can see the *leaves* and the forest," he says.

Sigal notes with a laugh that eyes are really, really complicated. They are full of fluid, and the amount of that fluid—and the pressure that its volume exerts—varies widely from person to person, as well as over the course of a lifetime, and even over the course of the day. The thinking, historically, was that glaucoma was the result of an excess of pressure pounding away year after year.

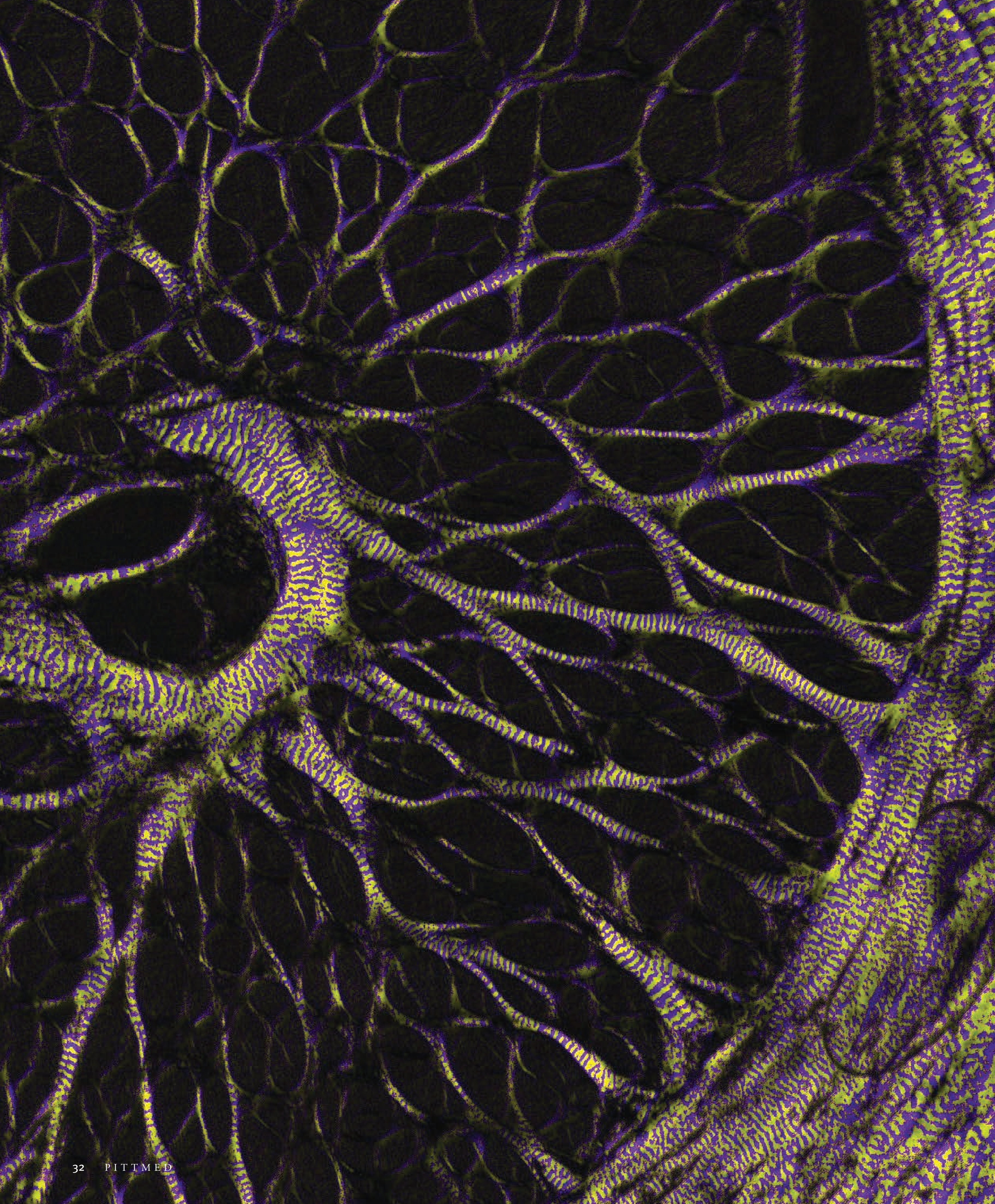
But as it turns out, research has revealed, plenty of healthy eyes have high pressure but never develop glaucoma.

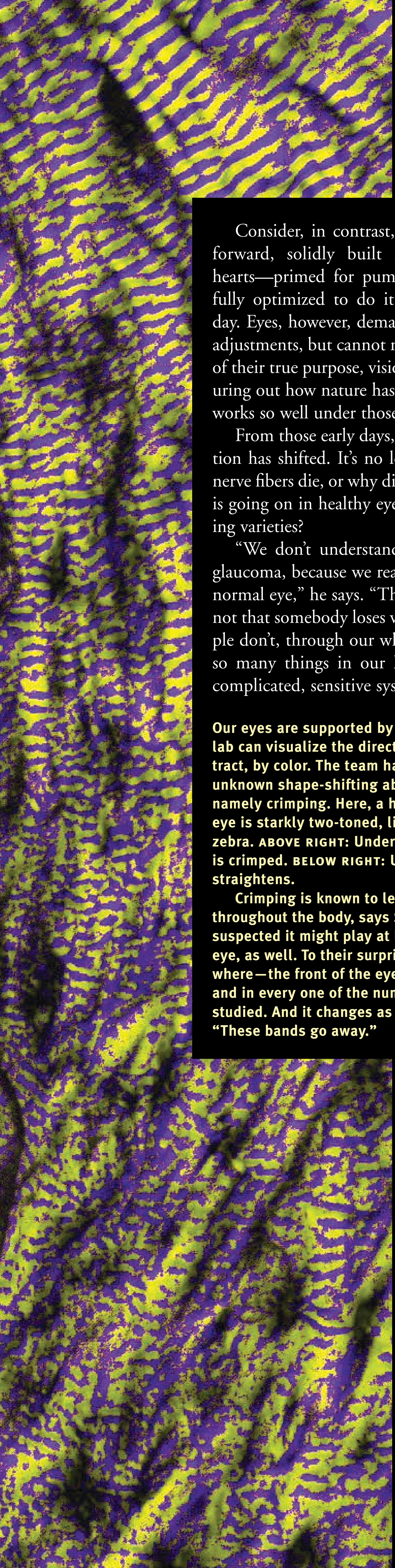
In computational and animal models, Sigal's team tested other possible explanations. For example, would shoring up the collagen—the supportive scaffolding of the eye—make the difference? And after careful study, the answer was: Nope, not necessarily. In fact, some eyes were even worse off for it.

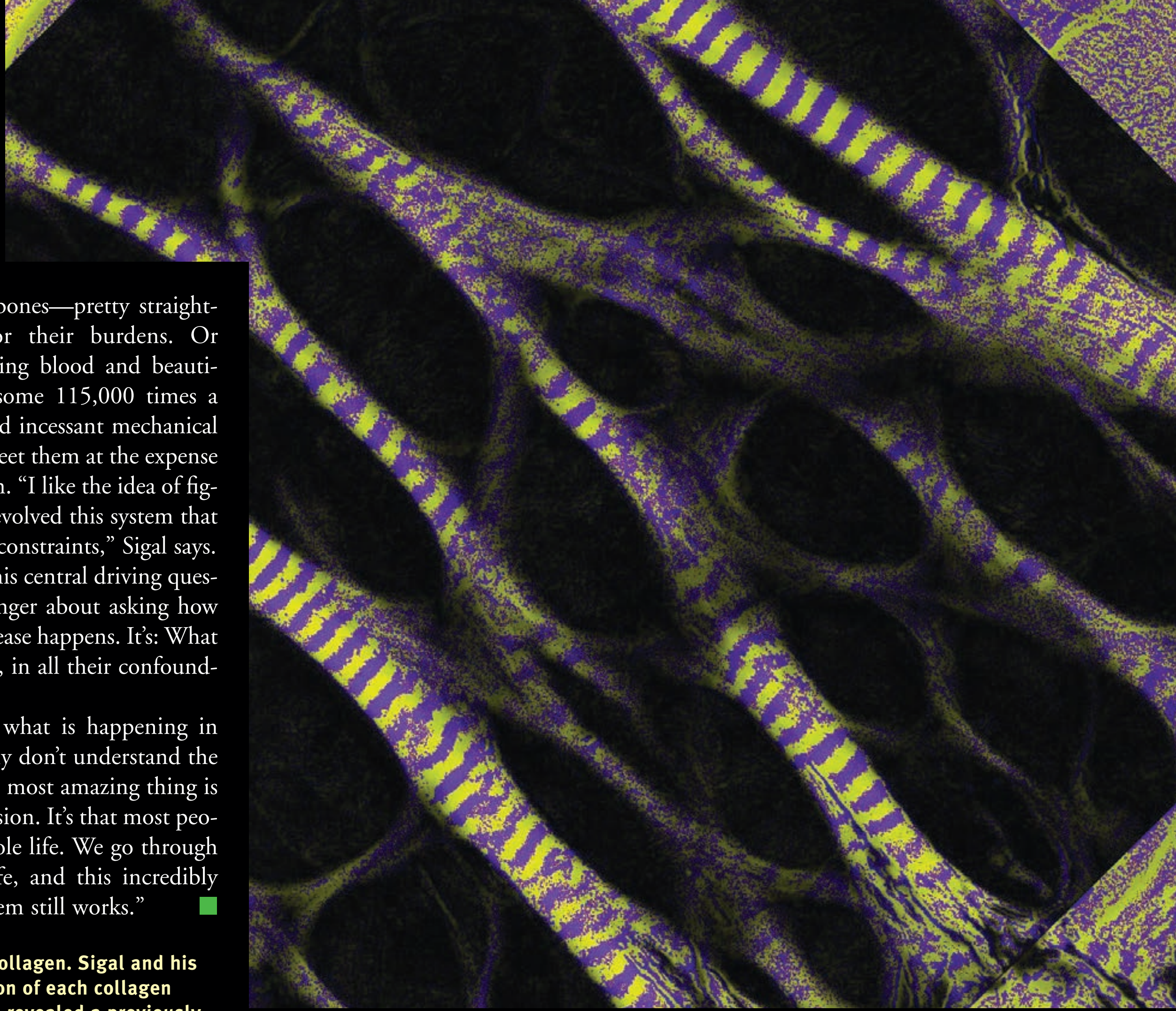
Over the years they've looked at lots of things that can go wrong with these structures: too stiff, too thin, too thick, too twisted, not twisted enough. No single factor seemed to serve as a measure of glaucoma risk. For just about every one of the structural varieties, there are people within the normal range who still got the disease.

The models grew increasingly complex over time, which made Sigal's job a lot harder, he says. But that was a good problem—and not just because he loves what he does. "Because when many things affect each other, you can have many ways for things to go wrong, and also many ways to fix them."

The eye tends to fix some things itself. For example, if the collagen becomes too stiff, it can decrease its thickness to balance things out. Or, if the lens or cornea in the front of the eye becomes too misshapen to properly focus the light, then the shape of the eye as a whole can lengthen out to compensate.







Consider, in contrast, bones—pretty straightforward, solidly built for their burdens. Or hearts—primed for pumping blood and beautifully optimized to do it some 115,000 times a day. Eyes, however, demand incessant mechanical adjustments, but cannot meet them at the expense of their true purpose, vision. "I like the idea of figuring out how nature has evolved this system that works so well under those constraints," Sigal says.

From those early days, his central driving question has shifted. It's no longer about asking how nerve fibers die, or why disease happens. It's: What is going on in healthy eyes, in all their confounding varieties?

"We don't understand what is happening in glaucoma, because we really don't understand the normal eye," he says. "The most amazing thing is not that somebody loses vision. It's that most people don't, through our whole life. We go through so many things in our life, and this incredibly complicated, sensitive system still works." ■

Our eyes are supported by collagen. Sigal and his lab can visualize the direction of each collagen tract, by color. The team has revealed a previously unknown shape-shifting ability of eye architecture, namely crimping. Here, a healthy 1-year-old sheep's eye is starkly two-toned, like a yellow-and-purple zebra. ABOVE RIGHT: Under low pressure, the tissue is crimped. BELOW RIGHT: Under high pressure it straightens.

Crimping is known to lend flexibility to tissues throughout the body, says Sigal, and his team suspected it might play at least a minor role in the eye, as well. To their surprise, they found it everywhere—the front of the eye, the back, the sides—and in every one of the numerous species they've studied. And it changes as eyes age, he says. "These bands go away."