

IN THE SERVICE



Clockwise from upper left: Anand Swaroop, Radha Ayyagari, Julia Richards, Paul Lichter, and Monte Del Monte

OF Sight

by Whitley Hill

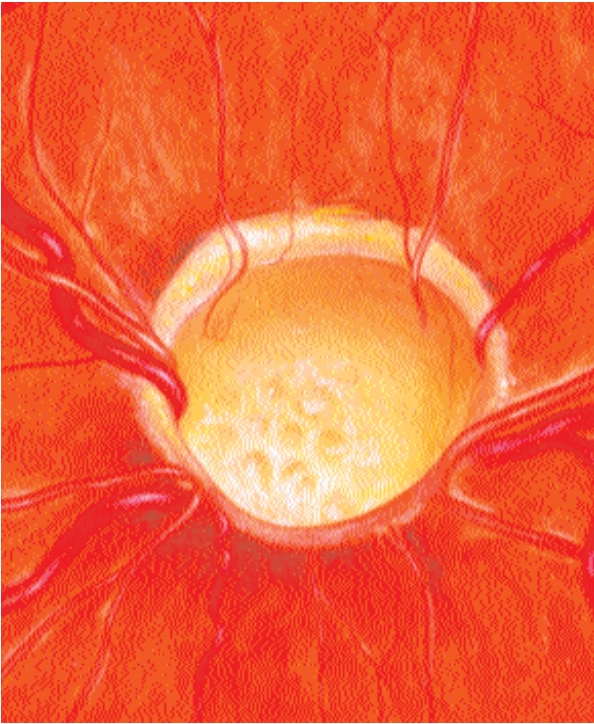
AT KELLOGG EYE CENTER, RENOWNED OPHTHALMIC RESEARCHERS JOIN FORCES WITH TOP CLINICIANS AND THE PATIENTS THEY TREAT TO PUSH THE BOUNDARIES OF VISION SCIENCE AND CARE

On an April afternoon in Ann Arbor 20 years ago, physician Paul Lichter and a small group of doctors, scientists and dignitaries gathered at a low-lying grassy field by the Huron River, near Ann Arbor's earliest town settlement, and stuck a shovel into the earth. After five years spent increasing the profile of ophthalmic medicine at Michigan, after earning the support of then-University President Harold Shapiro, and after raising millions of dollars in private and foundation funds, Lichter was ready to make the Kellogg Eye Center a place where research, teaching and healing would converge to create world-class vision care and research.

Today, he's getting ready to do it again.

"Back then, it would have been hard to imagine a day when the new building wouldn't be big enough," says Lichter, looking out from his seventh-floor window of Kellogg's signature "tower" with its sweeping view of the river and the U-M Health System, rising high to the east on the opposite shore. But that day has come. The labs and offices of the building are packed tight with brilliant people doing brilliant things on an array of sophisticated machinery. In the adjoining clinics, housed in a cheerful building that was once a nursing home, the demand for appointments is pushing the limits of clinical space.

Here is the cost of success: Kellogg has simply become too good to stay as it is. ➤



Gouache (opaque water color) painting of the retina of the eye showing advanced glaucoma with the optic nerve depressed. (Based on a photograph by Csaba Martonyi.)



Gerald Hodge

“The scientists we recruited as ‘rising stars’ 15 years ago are now in the mid-stages of their careers,” says Lichter (M.D. 1964, Residency 1968), chair of the Department of Ophthalmology and Visual Sciences and the F. Bruce Fralick Professor of Ophthalmology. “They’ve grown their programs and are full of ideas. We need to provide them space. And we have bright people pounding on our doors wanting to come to work here in this department.”

That research is at the heart of the Center’s growth. While some eye diseases have been tamed in recent years by understanding and high-tech treatment — cataracts, for example, can now be routinely removed and sight restored in an outpatient procedure, and new techniques and drugs are doing much to battle disease and preserve sight — other diseases continue to plague millions of people all over the world.

Julia Richards, Ph.D., developed a fascination with ophthalmic genetics in the late 1980s and saw an opportunity to participate in some intriguing and valuable work. “There was such a vacuum in this area,” she says, “so many problems crying out to be worked on.”

After initially exploring retinal genetics, an unexpected event shifted Richards’

focus. “The first year I was here, Dr. Lichter showed up one day wearing his white coat and carrying a little notepad filled with circles and squares and connecting lines. It was a pedigree, or family tree, of a particular glaucoma patient he’d seen. He gave me the page and said, ‘What would you do if you had a family like that?’ So I sat down and whipped out a little three-page prospectus and said, ‘If you were to do the following things, this family could be used to map the location of a glau-

Richards stresses that “glaucoma” is a very broad term, like “cancer,” and that there are multiple forms and many causes.

coma gene.’ And he said, ‘Go after it.’” Since that day, Richards and Lichter have collaborated in the hunt for genes that cause glaucoma.

As so often happens in science, another research team found their way to the gene first, but Richards was not discouraged. “Finding the gene is the beginning, not the end. At that point, there were a lot of questions: What is this gene? Why and how is it causing disease?” Her continuing studies of the gene in patients from all over the world

have helped provide information that will be important in genetic testing.

Richards stresses that “glaucoma” is a very broad term. “Ultimately,” she says, “glaucoma is a characteristic pattern of optic nerve death. But like ‘cancer’ or ‘infection,’ the term ‘glaucoma’ refers to a group of diseases with similar clinical manifestations but many different causes.”

In some people, there is increased pressure inside of the eye, Richards adds,

but there’s also “normal tension” glaucoma, undetectable by the eye pressure test one might take at the eye doctor’s office. “In normal tension glaucoma, the pressure’s in a normal range, and yet the nerves are dying. In the end, we’re going to need to solve all of these problems, but it’s going to take time and it’s going to take a lot of work by a lot of people.”

Richards and her team recently mapped the gene responsible for a rare condition called nanophthalmos, in which the

eyes are about 20 percent smaller than normal, but with a normal-size lens. The resultant crowding leads to glaucoma. They have also mapped a gene that causes corneal disease accompanied by glaucoma, and have cloned the gene responsible for a “syndromic” form of glaucoma in which multiple organ systems, including the eye, are affected by the gene defect.

Being at the University of Michigan has contributed to the successes of Richards’ glaucoma genetics projects, she says. “To have the clinician just down the hall from the electrophysiologist who’s right next door to the developmental biologist and the fellow who’s developing the transgenic animals and the biochemist who’s studying which proteins are carrying out various processes — this is powerful: all these people exploring different approaches to the same problem.”

Gerald Hodge is one of the lucky ones. His normal tension glaucoma was caught early during an eye exam at Kellogg, where extra-careful screening is simply routine.

“I think it probably would not have been found in many other places,” says Hodge, a retired U-M medical illustrator, “but the staff here is so exceptional. They found it and each eye was operated on. They put in a little valve under each upper eyelid to accommodate the pressure, and it’s been perfect ever since. The valves still function beautifully after more than 25 years. My visual acuity is still very, very good, and I’m 82 years old!”

Hodge takes out a book of slides and looks back on a lifetime spent drawing in great detail the miraculous structures of the human body. Vision loss is devastating to anyone, but Hodge says he shudders to imagine what might have happened had Paul Lichter, his doctor for many years, not diagnosed and treated his glaucoma. “I would have had to change professions,” he muses. “I was very lucky to be at a medical center where the ophthalmic department ranked as one of the best in the country.”

Age-related macular degeneration (AMD) is today the leading cause of blindness in the elderly population in the U.S., and with people living longer and longer, the number of those

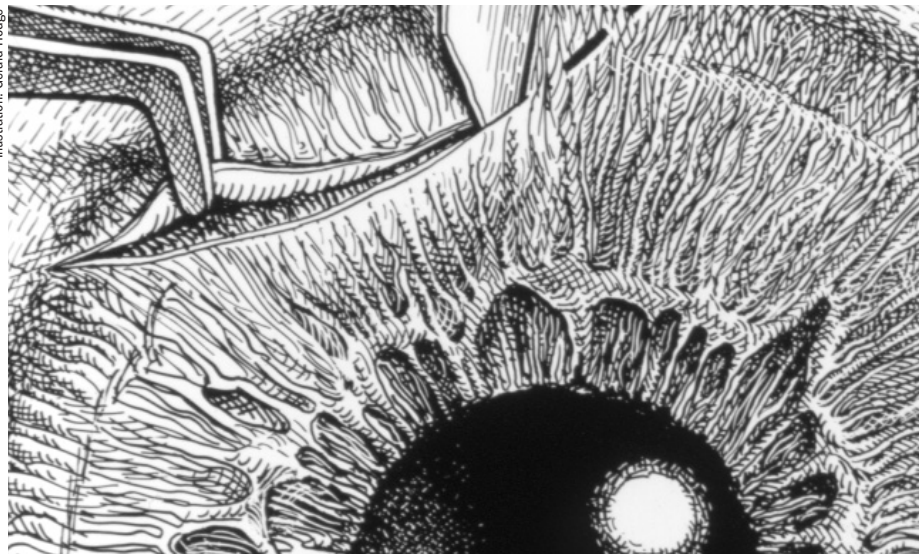
affected will continue to rise. The disease can be swift and stealthy. Often people simply wake up and realize that their sharp central vision is suddenly blurred. Words on a page appear swirled while peripheral vision remains normal. It steals mobility and independence at a time when many people are just beginning to enjoy the luxury of having more time for recreation. At Kellogg, a team of the world’s most renowned ophthalmic researchers have joined forces with top clinicians and the patients they treat to find a cure.

Like many Kellogg researchers, Anand Swaroop, Ph.D., a biochemist, molecular biologist and geneticist, was attracted by the opportunity to work in an openly collaborative atmosphere on projects that could help others. He was also

“It is clear that there is a genetic component to this disease,” he says. “But the problem is that by the time people get AMD, they are 65 to 70 years of age. It’s very hard to get large families to study. We don’t want to study just their children — they’re too young and we don’t know if they will have the disease — we want their parents, their siblings. And that’s not so easy to get. Still, we have collected a huge database here in Michigan, with over 1,500 people from 1,000 different families.”

Once affected families are identified, what practical, usable knowledge can be gained? For instance, does age itself alter gene expression or activity in people with AMD, causing damage to the retina? How can this be tested? According to Swaroop, one answer lies

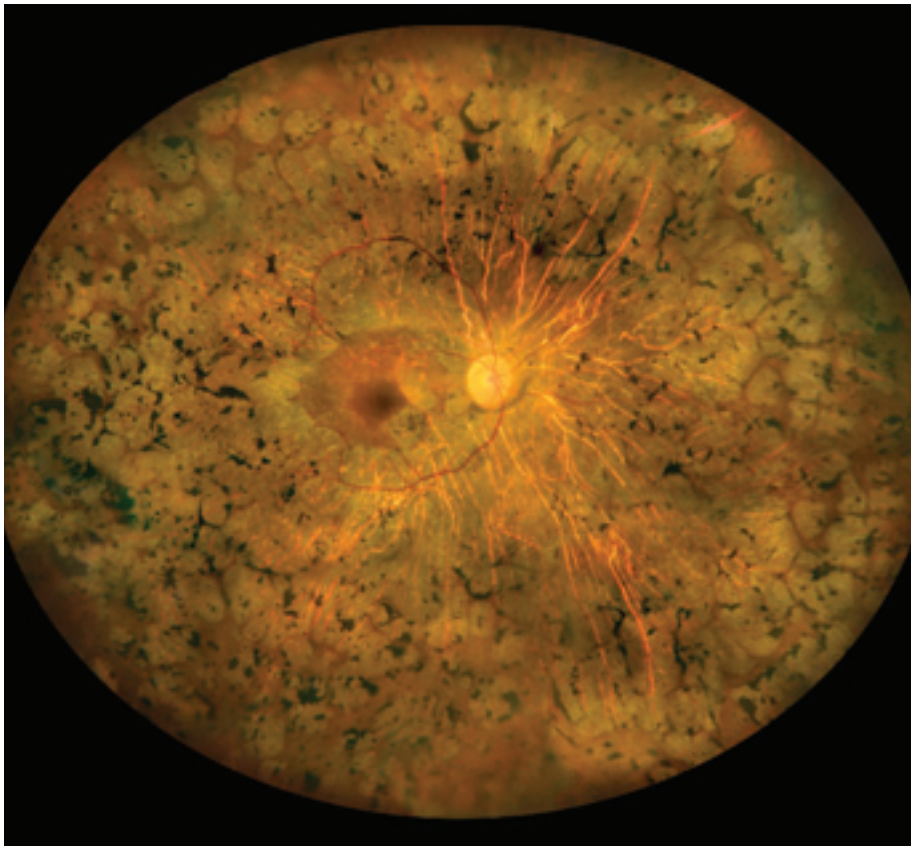
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Pen and ink drawing of an incision in the cornea for a filtering trephine operation for glaucoma.

eager to focus on the genetics of retinal and macular diseases. “I realized that the retina is nervous system tissue,” he says. “It’s a part of the brain, but it’s the most accessible part for functional studies and developing therapies.” Swaroop is interested in many different aspects of retinal research, from development and gene regulation to diabetic retinopathy. His work to unravel the mysteries of AMD has focused largely on the genetic basis of the disease.

within microarray technology, a relatively new technique for determining which genes are active in a specific cell. “We are one of the few eye centers in the country with this technology — it means we don’t have to look at one gene at a time. We can look at 10,000 or 20,000 genes at a time.” By using commercial microarray chips, as well as making their own — each containing thousands of tiny strands of eye genes — and flooding them with “messenger” RNA, ➤



A fundus map of retinitis pigmentosa, a hereditary condition, shows the typical extensive black clumping of pigment in the peripheral area of the retina and the attenuation of blood vessels as seen in the vascular arcade of the central retina. Fundus maps are created by compositing approximately 60 separate images taken with a retinal fundus camera.

It's Kellogg's national reputation at the pinnacle in ophthalmic care that makes it the first choice for people with serious or unusual eye problems, and when it comes to children that sentiment is even more pronounced.

Swaroop and his team can compare gene activity in retinal samples from young or old individuals, or from patients with AMD or another retinal disease.

"We want to use microarrays and animal models to understand the pathology of the disease process, identify new treatments, and find how effective they will be before we move on to humans," says Swaroop. "We moved from dream to reality on the AMD and microarray projects three or four years ago. We started from scratch, and now we're doing it, learning from it. As to the future, I'm a chronic optimist, but I'm also a realist. I see things changing dramatically in about 10 years, maybe sooner. First we will have gene-based diagnosis and hopefully methods for

slowing down the progression of disease. I definitely think in my lifetime, before I retire — *if* I retire — we will look at AMD and other untreatable blinding diseases differently."

Radha Ayyagari, Ph.D., is hoping to make inroads in the fight against age-related macular degeneration by looking at a rarer form of the disease that strikes much younger people, including individuals up to age 60. In 2001, Ayyagari and her collaborators mapped and cloned a key gene responsible for a form of early-onset macular degeneration that appears in the teen-age years. By studying this gene and the processes by which it steals vision in young people, she hopes to glean vital information that can be translated into effective treatments for millions of AMD sufferers.

More recently, Ayyagari and her team have been studying a particular early-onset macular degeneration gene that affects only males. Paul Sieving, M.D., Ph.D., long a Kellogg researcher and today head of the National Eye Institute, began studying a family with this mutation back in 1989. Since that time, the gene has been mapped to the X chromosome and has shown some surprising characteristics.

"Some mutations in this gene cause retinal degeneration which affects the peripheral part of the retina," Ayyagari explains, "but we found a specific type of mutation that affects only the macula, the region of maximum visual acuity. One mutation in this gene affects the peripheral part of the retina and another affects the center. By studying these mutations we hope to understand how one part of the retina is attacked and another part is spared."

Squirming on her mother's lap, a brown-eyed toddler stares hard at Monte Del Monte, M.D., the Skillman Professor of Pediatric Ophthalmology. She may not be able to see him, but she knows exactly where he is. As director of pediatric ophthalmology at Kellogg, this physician does groundbreaking research into diabetic retinopathy, leads ophthalmic residents to a greater understanding of their field, and pulls off some world-class baby talk in the course of diagnosis.

"Okaay... it's okaay..." he croons to the little girl as he looks into the back of her eye at the place where her optic nerve begins to thread its way to the brain. There is a problem and Del Monte does not mince words. Calmly and compassionately, he tells the baby's young parents, who have driven hours to get here, that for some unknown reason, their daughter's optic nerves have never fully developed. He encourages them to keep showing her things, to give her toys to play with, to let her watch television, to read to her, and to get in touch with their school district and begin low-vision therapy services as soon as possible.

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ON THE FRONT LINES OF VISUAL SCIENCE

AMONG THE KELLOGG RESEARCHERS TO WATCH...

Photo: Dave Renwick



The newest member of the Kellogg research faculty, Howard Petty is discovering how ultra high-speed imaging of cell activity in the eye can reveal much about these cell processes. Part medicine, part engineering, this technology may well be the new standard for ophthalmic imaging.

HOWARD PETTY, PH.D.

“I did similar work for 20 years at Wayne State, but the research is maturing and now I want to apply it in a more clinical setting. Kellogg is the perfect place to do that. In a real cell, under real conditions, all the small molecules and protons move about very quickly. With this imaging technique, we can see waves and patterns of chemical reactions within living cells that underlie the basic biology of the system. It may eventually help us to diagnose many eye disorders before they become clinically apparent.”

Photo: Gregory Fox

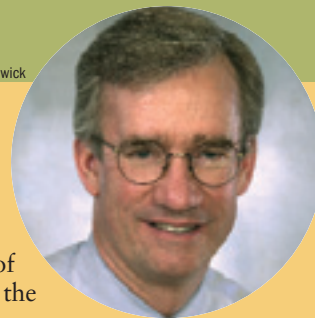


DAVID ZACKS, PH.D.

Retina specialist David Zacks joined the Kellogg faculty last September. He was recently awarded a Career Development grant from Research to Prevent Blindness to study the process by which certain retinal cells die during retinal detachment, a condition that causes severe vision loss and sometimes blindness.

“I’m very motivated in my research by the problems we see in the clinics. That really brings research alive to me. I think the expansion will take Kellogg from the great place it is now to being the premiere ophthalmic institution in the world. I have no doubt that we are on track to becoming the best eye center in the world. There’s no question in my mind.”

Photo: Dave Renwick



One of Kellogg’s most experienced retinal surgeons, Johnson is also deeply involved in conducting clinical trials for new drugs to treat macular degeneration. These drugs may be effective in stopping the growth of abnormal blood vessels that grow onto the

MARK JOHNSON, M.D. (RESIDENCY 1988)

retina and impede vision. He’s also the principal investigator in a series of studies to find drugs that can be injected into the eye or even implanted, to halt this devastating blood vessel growth.

“With increasing financial pressure on physicians, it’s important to be part of a group that is highly ethical. That’s one of the things I admire about the faculty at Michigan. They share a commitment to put the patient first, even to the point of not allowing drug companies or other industry representatives to come here to provide lunches. Patients can count on their interests being paramount when decisions are made about treatment.”

Photo: Martin Vloet



In her work with glaucoma patients, Moroi is all too aware of the delicate, often time-consuming process of prescribing the right drug at the right dose — a balance that ranges widely from person to person. As one of the rising stars in the field of pharmacogenetics, Moroi is learning how critically a patient’s genetic makeup can affect treatment options.

SAYOKO MOROI, M.D., PH.D.

“I’m looking at the complex interactions of several signaling pathways to try to understand why, at the ocular level, people are responding or not responding to drugs. And since Michigan is so strong in genetics, I can take it further to look at a genetic basis. The excitement about pharmacogenetics is that there is the potential for custom-designing therapy for a person based on his or her genetic profile.”



Krista and Bryon Anderson, their genetic counselor Katy Downs (standing), and Krista's guide dog, Anders

even more pronounced. “Any general ophthalmologist might see one or two children like this in the course of their practice. But with a referral base of this size, we see a patient like this every month,” says Del Monte after the family leaves. “So we become much more skilled at handling these rare things.”

Del Monte is yet another Kellogg physician who sees the planned building expansion as a compelling necessity. “This is a fine clinic, but it’s not anywhere near adequate. It’s shoehorned into a former nursing home. Our waiting space is too small. Since I came here in 1985, we’ve gone from doing about

100 surgeries a year to about 1,000. Office visits are now at about 10,000 a year, and we’re on a course to reach 12,000 soon, which is far more than this space can handle. We have community offices in Brighton, Livonia, Milford, West Bloomfield and Ypsilanti, but the patients from really far away usually come to Ann Arbor, where we have the full range of ophthalmic specialty care. We do a lot of inter-consulting on the same day. If someone’s here from, say, the Upper Peninsula — 10-12 hours away — and they need to have a retina check, I’ll call the retina specialists and say, ‘Can you see this patient today?’ And, of course, they will.”

When not seeing up to 50 patients a day in Kellogg’s Skillman clinic, Del Monte is working on the culture of retinal cells, studying their growth and their responses to various growth factors. His hope is that this work will result in improved treatments for diabetic retinopathy and retinal detachment.

From her pint-sized office, Katy Downs helps people make larger-than-life decisions. As one of Kellogg Eye Center’s two genetic counselors, her job is to take the complexities of genes, DNA, mutations, and heredity and lay them all out neatly for patients. Her clients: people whose family trees are dotted with cases of early-onset glaucoma, people with congenital cataracts who are thinking about having children, the parents of a little boy with a rare retinal cancer, all striving to understand why and how this could have happened, and to understand how best to look toward the future.

“As we identify more genes for eye diseases, and DNA testing becomes more available, a patient’s physician may be able to order a blood test to determine if that patient has a mutation that can cause a specific eye disease,” says Downs, “but it’s not that simple. In glaucoma, for instance, a patient might have the family history, get tested and find out he does not have the gene itself. But as a member of the general population, he could still develop glaucoma from other causes: a different glaucoma gene, trauma, reactions to other environmental triggers.” On the other hand, says Downs, although testing may confirm that the patient does indeed have the form of the gene that causes glaucoma, when and if the disease will be manifested, and how severe it might be, are, for now, unpredictable. Indeed, a patient with the gene might never develop glaucoma, but could still pass the gene on to a child who could develop the disease. Kellogg’s genetic research studies are addressing these issues.

As one of only a handful of ocular disease genetic counseling centers in the world, Kellogg is attracting patients from all over the country who are looking for someone to build a bridge from what is an almost incomprehensibly complicated science to understanding and appropriate, informed action. And with genetic knowledge growing expo-

nentially every year, the need for this service will likewise grow. To that end, genetic counseling at Kellogg will be dramatically affected by the upcoming expansion.

“We currently have a clinical molecular laboratory here that accepts samples from our patients as well as outside referrals,” Downs says. “At this time, we are accepting samples for a limited number of retinal diseases but the building expansion has the potential to make Kellogg a world-leading molecular diagnostic lab for many ocular conditions.”

Downs notes that her job doesn’t stop with the opening of an envelope that reveals a genetic test result.

“Genetic counseling is not just a matter of writing out a report, saying ‘This is the result of the lab test,’” she says. “We deal with a lot of uncertainty. The test results may not be able to predict the patient’s clinical course, and there are cases in which there is no testing available. Learning a part of one’s genetic make-up is new; we are the first generation to start to come to terms with this. We are the first to deal with the impact of molecular genetics on a person’s self worth, decision-making and identity. Genetic counseling is a dynamic process. We work with people in a way that addresses not just the scientific numbers, but the individual, too.”

Actually, Downs works with thousands of individuals, some of whom she has never met, some of whom are long deceased. As part of the research component of her job, she directs the family studies section of one of the largest glaucoma genetics studies in the world, mapping the pedigrees of Kellogg patients as far back as memory and health records permit.

A few years ago, a new client came to consult with Downs. Krista Anderson was then a young post-doctoral candidate at U-M, newly married and thinking of starting a family. But Anderson had some serious medical factors to weigh in making her decision.

“My family has a long history with the Kellogg Eye Center,” says Anderson, now a clinical psychologist practicing on the west side of the state. “My mother was diagnosed with congenital cataracts when she was a baby and when she had kids, she knew there was a 50 percent chance that her children



Instructor Sadashi Inuzuka works with Kellogg patient Mark Hymes during an art therapy session.

Expanded Kellogg facilities will be able to serve more patients, patients whose family histories will enrich more genetic databases, and whose participation in studies and trials will move ophthalmic medicine forward.

would develop them. She had our eyes checked; I was diagnosed at six weeks.” But modern cataract surgery was then in its infancy. And as can be common after this surgery, Anderson developed glaucoma. She was referred to Paul Lichter who was then just starting his career. Despite repeated surgery, she eventually lost all vision in her right eye.

“My understanding is that there’s a higher probability of developing glaucoma when you have congenital cataracts. My mother also has glaucoma. By the time I was 23, my glaucoma was out of control,” says Anderson. While living in Missouri, she underwent surgery for a detached retina and was left with only “10 to 20 degrees” of vision in her left eye. Today, she is assisted by Anders, an unflappable yellow Lab who accompanies her everywhere.

“When my husband, Bryon, and I began to think about having a family, we met with Katy Downs to talk about the chances of our children having congenital cataracts. She helped us to understand that this is an autosomal dominant

gene and that there would be a 50 percent chance that our child would get the cataracts. There are also better ways of dealing with cataracts than when I was a child. We explored adoption but ultimately made the choice to go ahead and have our children naturally.”

But there was another hurdle to cross. Paul Lichter was concerned about the possibility that Anderson’s already touchy eye pressure could elevate during pregnancy and perhaps rob her of her remaining vision. “It was heartbreaking,” she recalls. Anderson’s sister, whose vision is normal, made an extraordinary offer: surrogacy. Two embryos were implanted, from Anderson’s eggs and her husband’s sperm. And today, Bryson and Zoe are happy and active 14-month-old toddlers.

Anderson sighs, “Zoe does have congenital cataracts,” she says. “Bryson does not but Zoe does. I was very sad. We knew right away. She had her first surgery at Kellogg at two weeks. She wears soft contact lenses that act as the lenses of her eyes.” ➤

Little Zoe has also developed glaucoma and uses eye drops twice a day to help keep her eye pressure down. Her mother says she's grateful to Kellogg's genetic counseling program for giving her and her husband the information they needed to navigate some difficult life decisions, and for the fact that Zoe's early diagnosis has already helped to keep her vision healthy. "She sees very well. At her age I was already holding things up close." The whole story resonates with some larger truths as well. "You know, despite the fact that I'm legally blind," says Anderson, "I have lived a high-quality life and Zoe can, too. I feel very thankful for the care Zoe and I are receiving. We have to drive three hours each way to get to Kellogg, but I don't care."

Paul Lichter is a researcher, an educator, an administrator, a fund raiser and a strategist, but he's something else as well. "I still see patients," he says, after more than 30 years of practice. "I haven't been able to get the doctor out of me and I don't want to. I feel, in a sense, that society has a lot invested in me and those of us who are beneficiaries of that investment have a duty to use it as much as we reasonably can."

He says the new Kellogg building, which will actually be attached to the existing complex, can't not be built. "We will double our research program," he says. "The more people we can put onto a problem, the quicker we will get an answer. And we don't want to lose the people we have. They're always being recruited by other institutions, these scientists are so good. We want to keep them here, to grow the program here and make those crucial discoveries here, at Michigan."

He adds that at an academic medical center like Michigan, research goes hand in hand with education and patient care. The new building's increased clinical space will serve more patients, patients whose family histories will enrich more genetic databases, and whose participation in studies and trials will move ophthalmic medicine forward.

For all the looking ahead, however, Kellogg is very much a place where things are happening right now, from the most advanced science to simple human interaction, in the service of

'I have great admiration for the skills and abilities of Kellogg physicians...'

Helmut Stern is a businessman and art collector. That he still has the time and energy to chair the campaign to expand the Kellogg Eye Center is a testament to the man's extraordinary drive and commitment to the U-M Health System.

Born in Germany, Stern came to Ann Arbor in 1942 and, through a business associate, became acquainted with Alexander Ruthven, then president of the University of Michigan.

From Ruthven, the young Stern learned about the challenges of running a major American university. He also developed a respect for the institution that has led to a vital and enduring philanthropy. Today, that commitment is focused on two of the Health System's most important projects: the Cardiovascular Center and the expansion of the Kellogg Eye Center.

"I have a pretty broad interest as far as the University is concerned," says Stern, "but my interest in Kellogg was influenced in part because of my own eye problems. Fantastic work is being done in areas like glaucoma and macular degeneration. But we have an urgent need for additional space in order to be able to attract more high-caliber scientists and to give Kellogg Eye Center physicians and researchers the facilities they need to continue to do the outstanding work they are now doing."

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Helmut Stern

sight. In a special partnership between Kellogg and the U-M School of Art & Design, ceramicist Sadashi Inuzuka, himself legally blind, leads a free monthly art workshop for vision-impaired people of all ages. In the Center for Ultrafast Optical Sciences on North Campus, Gerard Mourou, Ph.D., one of the world's experts in ultrafast laser technology, collaborates with Kellogg researchers to find new ways to operate on the eye. Cheryl Terpening, the only full-time ophthalmic occupational therapist in the country, visits low-vision patients in their homes, helping them adjust and navigate a newly obscured landscape. In the Kellogg clinics, people who have struggled with simple near- and far-sightedness all their

lives are having their vision corrected through refractive surgery.

And in their labs, researchers like Julia Richards, Anand Swaroop and Radha Ayyagari keep working day to day, unraveling tiny mysteries that may be clues to a cure for macular degeneration, glaucoma, retinitis pigmentosa, or congenital cataracts. It is often frustratingly slow work, but the rewards loom large.

"We have this jigsaw puzzle laid out on the table," Richards says, "but only some of the pieces are there. We're trying to build up this picture that in the end is going to affect clinical care substantially. You know, science is like, 'baby step, baby step, baby step, LEAP!' I want to be here for the next leap!" 