Battling global blindness, eye disease through research

Photo by Ray Witlin/World Bank

About 39 million people in the world are blind, yet 80 percent of blindness is considered preventable. The National Eye Institute at NIH supports research into eye diseases that hit the world's poor the hardest, including trachoma, cataracts and other conditions.

Blindness is tragic wherever it strikes. For many in the developing world, it condemns them to a life of poverty with little chance to live independently. As much as 90 percent of the global burden of eye disease is shouldered by developing countries, where treatable diseases often go undiagnosed. About 39 million people around the world are blind and a further 246 million are unable to see properly, according to the WHO.

To help combat visual impairment and eye disease globally, as well as in the U.S., the National Eye Institute at the NIH supports a wide range of research studies. The NEI recently developed a new strategic plan to guide its activities in international research and global health. Its goals include establishing a full-time office devoted to the issue, fostering a sustainable research environment globally, expanding collaborations to advance vision research and supporting partnerships that add scientific value to NEI programs. In addition, the NEI intends to develop scientific capacity in the U.S. through training and mentoring to meet global health challenges and support vision research in the future.

NEI currently funds more than two dozen grants at 36 foreign sites in 15 countries. A number of these research projects focus on eye diseases prevalent in low-resource settings such as trachoma in Ethiopia and Tanzania, glaucoma in Ghana and corneal ulcers in India. Meanwhile, scientific collaborations in developed countries are probing a wide range of specialities from retinal stem cells in Canada, to diabetic retinopathy in Denmark, to pediatric eye disorders in the U.K.

About the NEI

THE NATIONAL EYE INSTITUTE is one of the 27 institutes and centers that constitute the NIH. Its director is Dr. Paul A. Sieving. NEI has the mission to conduct and support research, training, health information dissemination and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight and the special health problems and requirements of the blind.

Established by Congress in 1968, the NEI supports approximately 1,600 research grants and training awards made to scientists at more than 250 medical centers, hospitals, universities and other institutions across the country and around the world. The NEI also conducts laboratory and patient-oriented research at its own facilities located on the NIH campus in Bethesda, Maryland.

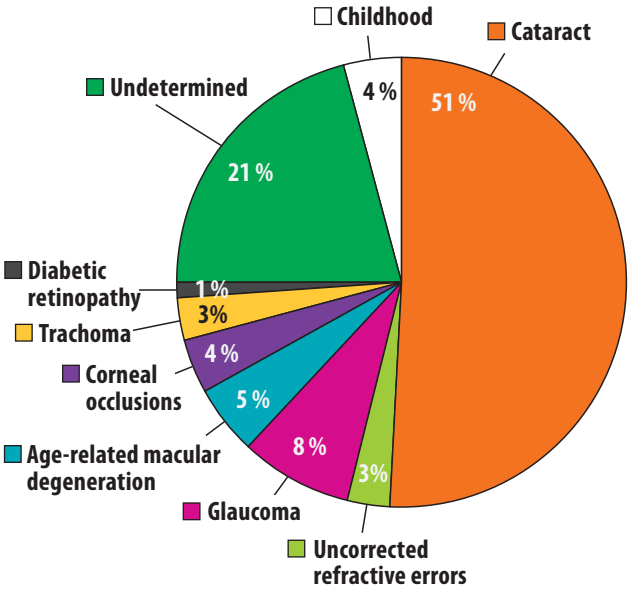
The National Eye Institute currently funds more than two dozen grants in 15 non-U.S. countries, supporting global health research in genetic, infectious and environmental eye diseases.

Photo by Alan Gignoux/World Bank

This section was produced by Cathy Kristiansen, with contributions from Christopher G. Thomas, Tom Hoglund and Richard S. Fisher.

In addition, the NEI has been collaborating with the WHO since 1979 to build research capacity by pairing experienced investigators with local scientists to study an eye health problem in that country. This collaboration has produced some 30 scientific publications about topics such as visual impairment in school-age children in developing countries and the evaluation of eye care services and the burden of poor vision and blindness in Brazil.

Global eye disease



Source: The WHO

Photo by Chris de Bode/WHO

India and China suffer high numbers of blindness. The National Eye Institute supports collaborations, partnerships and training programs with these countries and several others in research to prevent blindness.

Turmeric improves eyes

Photo by Jeff Gray

Retinitis pigmentosa is a group of degenerative eye diseases caused by genetic mutations that lead to severe vision loss and blindness. Worldwide, more than one person in 4,000 is affected. Current experimental gene therapy involves injecting healthy copies of the culprit gene into patients' eyes. Although early clinical trials are promising, this approach is expensive and challenging, with more than 45 genetic mutations identified.

Recently, NEI-funded researchers found that curcumin, the active ingredient in the spice turmeric, may treat some forms of retinitis pigmentosa. A study led by Dr. Radha Ayyagari, associate professor of ophthalmology at the University of California, San Diego, showed that curcumin prevented the abnormal and damaging protein build-up usually caused by a mutant gene.

The researchers investigated the P23H gene governing the protein rhodopsin, which eye rod cells need to detect light. With this mutation, the protein accumulates and eventually kills the cells. Previous research showed that curcumin inhibits build-up of the protein amyloid beta, thought to contribute to Alzheimer's disease.

The team found curcumin prevented mutant P23H rhodopsin from abnormally clustering in laboratory-cultured cells, so they fed the compound to rats genetically engineered to have the mutation. These rats, unlike control animals, showed reduced protein accumulation, which in turn preserved the number of retinal rods and cones and increased the light-induced electrical response in the rats' eyes.

Another benefit of curcumin is that unlike many drugs, it crosses the blood-retinal barrier, a protective meshwork of cells surrounding the retina. The researchers found curcumin had reached the rats' retinas after only two days of feeding. This suggests that patients with retinitis pigmentosa could simply take curcumin pills or include turmeric in their diet, rather than have a drug or a gene surgically injected into their eyes.

Unusual protein clustering may also be linked to eye diseases that affect other cells in the retina. The results reported by Ayyagari and her colleagues suggest that curcumin could treat all of these cases. But further work is needed to back up these preliminary findings and test which curcumin dosages are most effective.

RESOURCES

Full article: http://1.usa.gov/RDmd3u

Research shows path toward trachoma elimination

Repeated mass treatments with antibiotics can greatly reduce the occurrence of trachoma, a bacterial eye infection that causes blindness in millions of people, NIH-supported research has shown. In addition to paving the way to eliminate the disease, which largely strikes developing countries, studies indicate the therapy also protects communities from other infections, reducing child deaths from pneumonia, diarrhea and malaria by 50 percent.

After years of targeted funding and research, trachoma has been wiped out in some regions and the WHO aims to vanquish it in remaining places by 2020. Research funded by the NIH's National Eye Institute (NEI) is playing a crucial role by identifying effective antibiotic regimens to combat the scourge. These include determining how often to administer treatment, what portion of a community must be reached and how to prevent re-infection.

The main treatment for active trachoma, caused by the *Chlamydia trachomatis* bacterium, is the antibiotic azithromycin. Mass treatment became economically feasible only in 1998 when the International Trachoma Initiative began making substantial quantities of azithromycin available at no cost. "We now had a single-dose antibiotic, which provided the impetus to fight this disease," recalls Dr. Sheila K. West, NEI grantee and professor at Johns Hopkins University.

The National Eye Institute at the NIH supports research to determine the most effective ways to deploy antibiotics to eliminate trachoma, which currently affects about 40 million people, mostly in the developing world.

Photo by Raul Vasquez/ORBIS

The idea of treating entire communities at once is similar to vaccination programs against diseases such as polio and typhoid. Both infected and non-infected individuals in a community are inoculated, to reduce the pool of infection and prevent the eruption of new cases. Unlike vaccinations, though, mass treatments with antibiotics typically need to be repeated numerous times.

Studying ways to prevent infection

This raised questions of how frequently and for how many years treatments should be administered to keep infection at bay. It might be impossible to reach every person in a community, so how widespread did the treatment need to be to produce "herd immunity," as in vaccination programs? Should only children receive the antibiotic or also adults? Would periodic mass treatments with antibiotics increase the risk of drug resistance?

NEI focused on these important issues, funding researchers to conduct several large community-based studies in different locations with widespread trachoma infection. Early results showed a single mass treatment with azithromycin reduced disease prevalence in a community, but infection returned within a year in the most severely affected areas. Another study tested the impact of multiple mass treatment rounds and found communities needed more than seven—and perhaps as many as 10—annual mass treatments to conquer trachoma. Subsequent trials confirmed that long-term reduction and even elimination of the disease is possible with repeated mass antibiotic treatments involving most residents of a community over several years.

> "Elimination (of trachoma) will be an enormous task, but the treatment and prevention approaches needed for success are now more clearly defined."

"By giving treatment on an annual basis, you eventually catch up and prevent the disease from flourishing," West said. "The question now is not so much how frequently you do it, but whether you can get away with treating just kids versus treating everybody."

Meanwhile in Ethiopia, NEI-funded researcher Dr. Thomas M. Lietman led a clinical trial involving 24 communities to determine whether mass treatment of children younger than 11 would protect the entire population. Working in collaboration with the Carter Center and the health ministry, Lietman discovered after one year that trachoma occurrences among children given azithromycin had plunged from 48 percent to less than 4 percent. Infection also dropped significantly in older, untreated children and adults, suggesting that repeatedly treating younger children might be a cost-effective strategy to control infection throughout a community.

Not only did the antibiotic ward off eye disease, but Lietman and his colleagues discovered another benefit—child deaths dropped by half in treated communities, suggesting that azithromycin helps mitigate potentially lethal infections such as pneumonia, diarrhea and malaria.

However, the potential for drug resistance to antibiotics is a key concern. Studies have shown the bacterium *Streptococcus pneumonia* is capable of building resistance, but the risk diminishes several months after treatment. The long-term effect of administering multiple rounds of azithromycin is still unknown.

Preventing blindness and re-infection

Repeated trachoma infections often lead to trichiasis, a condition of turned-in eyelashes that scratch the eyeballs to the point of blindness. In such cases, mass antibiotic treatment does not prevent vision loss, although surgery can. Yet, trichiasis recurs in half of post-surgical cases. To improve outcomes, the NEI funded the Surgery for Trichiasis, Antibiotics to Prevent Recurrence (STAR) trial. West and her colleagues in Ethiopia randomized one group of patients with trichiasis to receive azithromycin after surgery; the other group received standard postsurgical care, which involved topical tetracycline ointment. Azithromycin reduced overall trichiasis recurrence by one-third and severe trichiasis recurrence by almost half, compared with standard treatment.

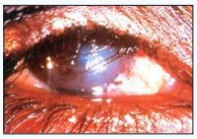
NEI-funded research over the past decade has answered these and other scientific questions necessary to tackle trachoma, laying the groundwork for other organizations to become involved in elimination efforts. For example, the Bill and Melinda Gates Foundation has awarded $12 million to Johns Hopkins University to continue its work. With more than 40 million people suffering from trachoma throughout the developing world, elimination will be an enormous task, but the treatment and prevention approaches needed for success are now more clearly defined.

"NEI stepped up to the plate early on by funding trachoma research, hoping that would lead to other partners to come in and fill in the gaps, and that has now happened," West said. "The goal of elimination of blinding trachoma by 2020 will be a challenge. Research to inform programs on strategies to achieve that goal will be a key component to success."

Photo by Kiran Ridley/ORBIS

Trachoma is the leading cause of preventable blindness. It spreads through contact with hands, clothing or flies.

Blindness from trachoma and trichiasis



Trachoma is currently the leading infectious cause of preventable blindness worldwide. Repeated, untreated infections over years build scarring on the inside of the eyelids and make the eyelashes turn in—a condition known as trichiasis. This scrapes and irritates the cornea, compromises vision and eventually causes blindness.

Trachoma remains a significant public health concern in many developing countries, especially in regions that suffer from overcrowding, water shortages and poor hygiene. Infection spreads from person to person, usually among children, through contact from hands, clothes, or flies that carry discharge from the eyes. Due to their close contact with children, women suffer three times more infections than men.

The WHO estimates that 40.6 million people suffer from active trachoma and 8.2 million have trichiasis. Hardest hit areas are in the Middle East, North and sub-Saharan Africa, India, Southern Asia and China. To tackle this misery, the WHO launched a trachoma elimination strategy, called "SAFE," involving trichiasis surgery, antibiotics and improved hygiene, which it hopes will succeed by 2020.

RESOURCES

Article: http://1.usa.gov/RThmKc
Website: www.vision2020.org

Vision research leads to new theories on brain plasticity

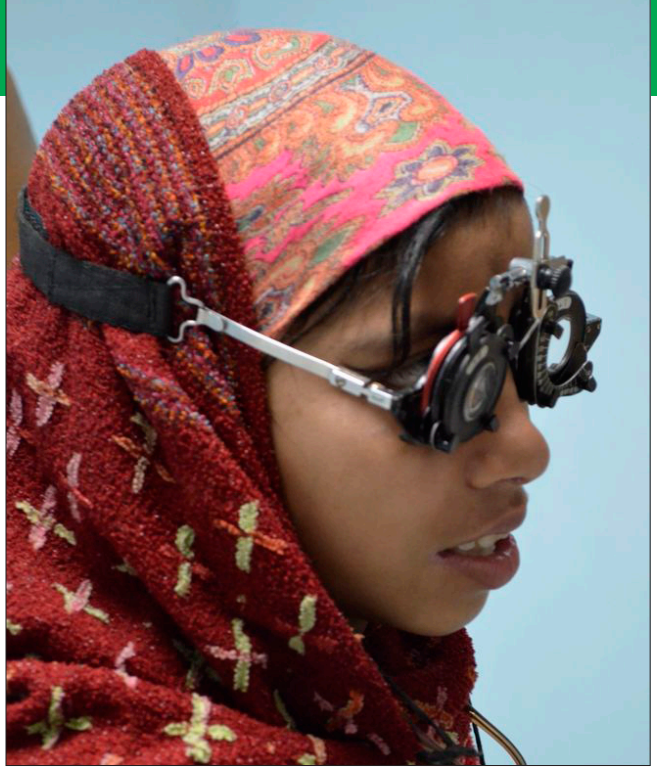


Photo courtesy of Dr. Pawan Sinha/Project Prakash

With research funding from the NIH's National Eye Institute, Project Prakash has made discoveries about brain plasticity that may lead to new approaches to treat deafness and autism.

A baby was born blind in a small Indian village. His parents assumed he was just another victim of the family curse, destined to a life without sight like his sister, father and grandmother before him. Blindness is all too common in India, striking one in 100 people.

The parents, resigned to his fate, sent the boy to an institution for the blind when he was four years old. His world changed inexorably a few years later, when health workers visited his school to conduct screening tests and determined his eyes were treatable. He soon underwent surgery and at last began to see. The scientists monitoring him were astonished to observe his post-surgery vision develop in ways that earlier research had deemed impossible. This discovery not only challenged established views on brain plasticity but may also lead to new approaches for children with deafness or autism.

The boy's screening and surgery were provided at no cost by Project Prakash, a nonprofit organization established in India to diagnose and treat people with curable blindness. It was founded by Massachusetts Institute of Technology neuroscientist Dr. Pawan Sinha, who was moved to act by a chance encounter with a blind person during a visit to his native India. Begun as a humanitarian program, Project Prakash led Sinha to make surprising discoveries about how the brain develops and humans learn to see. "Prakash," the Sanskrit word for light, signifies both bringing sight to children and illuminating scientists' understanding of brain development.

By treating children and young adults, allowing them to see for the first time in their lives, Sinha has had a unique opportunity to study how the brain learns to process color, shape and movement. "The population of individuals who are blind from birth and who have treatable conditions—these are extremely rare cases in the West," Sinha noted. His patients provide a unique window into the process of visual learning, enabling him to monitor the entire process from day one. Babies are not good research subjects because by the time they can communicate, they've already passed key developmental milestones. Project Prakash patients can verbalize their experience and remain still for brain scans, so scientists can observe how different parts of the brain engage during vision tests.

What Sinha and his colleagues have discovered has turned earlier scientific notions on their head. For many years, researchers believed there was a developmental window for vision that closed at around six years of age. They thought anyone blind from birth would not be able to acquire much visual proficiency if they gained sight later in life. Sinha's patients have forced reconsideration of those theories.

"Project Prakash is not just benefiting the children who are being treated, but it's likely to have far greater consequences," Sinha said in a recent interview. "That one can directly combine a medical humanitarian intervention with basic science, it's a powerful idea."

Since 2006, the NIH's National Eye Institute has provided research funding to Project Prakash, which has been "critical" to its success, Sinha noted. Based at the Shroff Charity Eye Hospital in New Delhi, the venture has so far screened more than 20,000 children and surgically treated at least 400 with curable conditions. Many more have received non-surgical care, including glasses. Its findings have also led to a petition in India's Supreme Court to ensure that every child in the country must be examined by an ophthalmologist before admission to a school for the blind.

Children encountered by Project Prakash have not previously undergone screening or treatment for a variety of reasons, including limited family finances, religious beliefs, distance to hospitals and old theories that sight cannot be recovered after a certain age. "Many parents really don't know whether the blindness that their child has is a treatable condition or not. Some of them believe it is just fate," Sinha said.

Project Prakash research has revealed the brain has significant capacity to "catch up" in interpreting color and light signals to recognize objects, regardless of whether the

window was dark during the early stages of development. For example, Sinha led one study on object recognition involving three participants, all of whom had gained vision after the age of six. They tried to identify a variety of simple objects displayed on a computer screen. For three months after treatment, they could recognize some objects displayed separately, such as a triangle or a circle, but tended to identify a third object when the shapes overlapped.

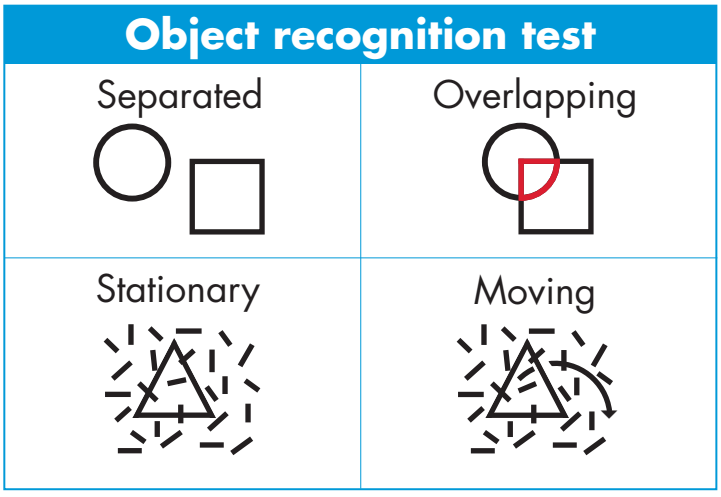
Additional tests showed that motion aids the brain's ability to distinguish individual objects, which was a key finding in the science of blindness. For example, the participants could see a triangle displayed among scattered lines more readily when it constantly moved than when it was stationary.

Whether blind people can, on gaining sight, immediately learn to visually recognize objects they previously knew by touch has been a mystery. Sinha and his colleague Dr. Richard Held conducted a series of experiments that showed the brain rapidly—even within a week of surgery to repair the eyes—starts mapping information across the senses about how an object looks and feels.

Project Prakash also uses functional brain imaging pre- and post-operatively to see how children's brains are organized and function in the weeks and months after surgery, Sinha said. Project Prakash studies "are giving us unprecedented and extremely valuable information about how the scaffolding of vision gets set up. They inform our conceptions of basic neuroscience and may be relevant for how we can tackle some neurological problems, conditions that require an understanding of brain mechanisms of plasticity."

Courtesy of Dr. Pawan Sinha/Project Prakash

By studying how previously blind children in India learn to see, MIT's Dr. Pawan Sinha has discovered the brain is more adaptable than previously thought.



Among the other fields of science taking a cue from Project Prakash findings is autism. "Some of the visual impairments that have been reported in the domain of autism are very similar to the kinds of impairments we find in the Prakash children soon after they gain sight," Sinha said. "We are trying to find out whether this is a superficial or coincidental similarity or something deeper."

Sinha has studied 40 children with autism, testing their visual and auditory patterns, and identified deficits in temporal integration. "Even though superficially autism has very little to do with congenital blindness, it can benefit from the same kind of model as Project Prakash, merging the provision of medical care with the opportunity to learn more through research," he added.

Another potential application is with deaf children. "Exactly the same sort of idea would apply to deafness as to blindness: Would the brain of a child who has been deaf from birth be able to acquire auditory processing capabilities, would he be able to acquire spoken language even if he is treated several years after his birth?," Sinha wonders.

As for the children who are currently untreatable because of damaged eye structures, Sinha dreams that one day they will gain eyesight as well. "Having cortical prostheses is way down the road, but at least conceptually, one can imagine feeding information derived from a camera directly to the cortical regions of the brain and enabling vision."

The light shining from Project Prakash is reaching other developing countries with high numbers of blind children—such as Brazil, Pakistan and China—where officials are studying Project Prakash so they can replicate its success.

For the blind boy who had cataract surgery at age seven, his eyesight now measures 20/100. Within ten months of his operation, he'd learned to see and identify static objects. For him, and a growing number of Project Prakash patients, the light now glows brightly.

RESOURCES

Project Prakash website: http://bit.ly/PPrakash
NEI article: http://bit.ly/SsPpEr
ITC Bookman Std NIH lecture: http://1.usa.gov/Qt2YKM

Q&A

DR. GYAN ("JOHN") PRAKASH, PH.D., M.B.A.

As associate director at the National Eye Institute's Office of International Programs—Office of Global Health, Dr. John Prakash plays a key role in overseeing his Institute's international involvement in eye disease research and training. He previously held senior positions at AMAR International and Pfizer Pharmaceuticals' International Division. He earned a Ph.D. in microbiology from the University of Illinois at Urbana-Champaign, and received postdoctoral training in biotechnology at the University of California, Los Angeles, Medical School and the CDC. He earned an M.B.A. in pharmaceutical management at St. Joseph's University in Philadelphia.

What is your perspective on the need for global health research into eye conditions?

Eye conditions affect so much of the population at some point in our lives, whether at birth; as we age, as with macular degeneration; or as a condition brought on by another disease, such as diabetes. That's what makes the research we conduct and support so essential. And we at NEI are committed to taking a global approach. The vision research community is very active in many parts of the world—such as China, India, Brazil, the U.K., Germany and many other countries—and we are looking for discoveries from wherever they may arise. International research can inform us about diseases that are prevalent in many different parts of the world.

Overall, we are emphasizing high-quality science, including molecular biology, genetics and clinical research programs, where we can collaborate and learn from the scientists who are driving the research advances. For many years, NEI has fostered an active interest in international research, collaboration and training, managed through a special office within the Institute. Today, one of our main goals is to sustain a vigorous international research environment, expand collaborations in vision research among different countries and support international partnerships that are providing scientific value to the NEI programs.

How does NEI research address the enormous disease burden in low- and middle-income countries?

Eye diseases are prevalent around the world. No area is free from blindness, although most blindness occurs in developing countries. What's more, up to 80 percent of blindness is preventable. We want to work with the global research and health care communities to stop vision loss before it happens. Much of what we learn about eye health comes from performing global research and from studying specific patient populations, such as pediatric or elderly patients. Country- or region-specific research might provide more in-depth answers to the causes of blindness.

What is the makeup of NEI's international and global portfolio?

We have underway more than 50 international collaborations, projects, affiliations and other engagements on all six continents. The heaviest concentration of our collaborative engagements is in Asia, which accounts for about 40 percent, while 35 percent of our global initiatives are in Europe and the rest are elsewhere. In India, for example, the Aravind Eye Hospital is working with the U.S. Cleveland Clinic to identify primary open-angle glaucoma biomarkers. And Harvard University is collaborating with the L.V. Prasad Eye Institute to develop pluripotent stem cells for eye diseases and with Sankara Nethralaya in genetic studies. It's a very exciting time to be working in this area.

How does NEI plan to foster the next generation of global health scientists?

One of NEI's key global health goals is to develop human capital in the U.S., so we're ready to meet whatever needs arise in vision research and training. This means supporting excellent mentors to train the next generation of scientists and professionals. In fact, the NEI has a record of training numerous scientists in our intramural labs who have returned to their original countries. Several have become leaders there. We are currently training 66 international scientists and fellows in NEI's intramural labs, generally one or two from a given country, but 16 from China, 15 from India and 8 from Korea. In the past two years, 18 trainees have completed their studies and returned to their homes to continue their careers in global health and vision research.

We also manage an NIH-wide effort, the Khorana-Nirenberg Scholars Program, to train scientists of exceptional ability and potential as leaders in their countries. The training is in any field, not necessarily eye research. Once they are established in their countries, there is a high probability they will continue to conduct research, train others at home, and create long-term partnerships, including many with colleagues in the U.S.

PROFILE

Fogarty fellow tackles inherited childhood glaucoma in Nigeria

Photo courtesy of Dr. Fafowora

Former Fogarty Fellow Dr. Oluwatoyin Fafowora is studying the genetic basis for juvenile-onset glaucoma, which is prevalent in West Africa.

In the ophthalmology practice, one patient stood out: a young man diagnosed with glaucoma who doggedly pursued a career as an accountant until he could no longer see. He had a hereditary form of glaucoma that typically develops much earlier in life than the well-known adult-onset type, and that currently is resistant to medical and surgical treatment.

"You are seeing a 15-, 17-, 20-year-old who has his life mapped out before him and you discover he is going blind from juvenile-onset glaucoma," said Dr. Oluwatoyin F. Fafowora, a former ophthalmology clinical practitioner, who was moved by her patient. "Because it affects the younger generation, I found it rather painful to be treating it. I very much prefer research. It's more meaningful."

Oluwatoyin F. Fafowora, M.D., M.P.H.	
Fogarty Fellow:	2008-2010
Fellowship at:	University of Ibadan, Nigeria
Research focus:	juvenile-onset glaucoma
Website:	http://1.usa.gov/STgSpz

The door to research opened when she received a Fogarty fellowship in 2008 to engage in global health studies. Fogarty's Global Health Program for Fellows and Scholars offers postdoctoral and doctoral students the opportunity to spend a year collaborating with a mentor at an established research site in a developing country. The experience is intended to encourage early-career scientists to pursue global health research, provide a training resource to the host institutions and nurture international research partnerships.

Under her fellowship, managed by the University of California, Los Angeles (UCLA), Fafowora returned to her native Nigeria to investigate potential genes behind the specific condition that had struck her young patient—juvenile-onset open-angle glaucoma. This form of glaucoma is prevalent throughout West Africa, allowing her to tap into a larger pool of patients than would be possible in the U.S. Fafowora led a team at University College Hospital in Ibadan that tracked down families with a history of the disease and collected samples of their DNA.

Earlier research identified about seven candidate genes and Fafowora sought to confirm their involvement and identify additional genes. Her project showed such promise, her fellowship was extended for a second year.

She says she discovered research is very different from clinical work and she had to quickly learn a range of new skills during her fellowship. "You have to decide the importance of the disease, the feasibility of studying that disease, the usefulness of the outcome. And also what is important to you and to the funding institute," she said. "Then writing the proposal itself was a good experience."

For her project to succeed, she needed help on the ground in Nigeria. "My collaborator and I have been able to work together almost seamlessly and that helps open up a new vista. You can achieve more than if you were working individually." In addition, advice from her Nigerian and UCLA mentors kept her project on track. "They could see further down the road than I could, so they could help to iron wrinkles out before they arose," Fafowora said.

She's still working to complete analysis of the data to pinpoint genes that bring a high risk for this type of glaucoma and then hopes to publish her findings. Once the relevant genes have been identified, children can be screened for them. "Then you have a much better chance of preserving vision." Fafowora said. "We hope our findings will contribute to the development of gene therapy for glaucoma."

Today, Fafowora is a research fellow at UCLA's Jules Stein Eye Institute, studying for a doctoral degree in epidemiology. She hopes that ultimately, with her strong clinical background and expanding research skills, she'll contribute to a wave of discoveries that will end blindness from inherited glaucoma. "I'm in research now and I like it. I want to work to find new knowledge, to make a difference."