What are the most important basic questions that remain unanswered in the field of glaucoma?

Glaucoma is really a disease of two tissues: (1) the outflow pathway through the trabecular meshwork and Schlemm canal and (2) the optic nerve or ganglion cells. Fundamentally, what causes the disease in either of these two sites? Whereas all current glaucoma therapy works by lowering the IOP in a nonspecific manner, medical school taught us to identify the diseased tissue and try to intervene at the tissue level to restore normal function. Although current medications are more potent than earlier agents at lowering the IOP, the fact that they are not specific to what causes the IOP to rise means that, with time, the pressure will drift upward and the patient will need new therapies.

A related question regards how to discern the earliest signs of glaucomatous damage to the optic nerve or ganglion cells, because we are unable to detect early phases of the disease. We cannot differentiate patients who only have an early elevation of IOP from those who also suffer early, subtle glaucomatous damage.

Another important question is how can we accurately and continuously monitor IOP? Patients visit the ophthalmologist’s office only once or twice per year. The ophthalmologist can accurately measure IOP, but that pressure can fluctuate diurnally and certainly throughout the week. Although we know that an IOP measurement is only a 1-second piece of data, we all tend to think it is the representative IOP since the last time we saw the patient. As a result, there are some puzzling instances of glaucomatous progression despite an IOP that seems okay.

Finally, why are some patients’ optic nerves and/or ganglion cells more susceptible to damage at low levels of IOP? It is difficult to set an appropriate target pressure for such patients until they continue to show damage, a somewhat backward approach to the problem.

What are the goals of your current research, and has anything surprised you about your work thus far?

The primary focus of my career has been to try to understand how the trabecular meshwork normally functions, identify what causes glaucoma, and develop therapies directed at this diseased tissue that will cure the IOP element of glaucoma. We do not know what causes glaucoma in the outflow pathway or even how the aqueous humor normally exits the trabecular meshwork. Neither do we know exactly what the cellular pathway is or how this process is regulated. I am very interested in the optic nerve, but my position has always been that the optic nerve and ganglion cells are really part of the brain. It ought, therefore, to be easier to try to understand the normal and abnormal function of the trabecular meshwork in glaucoma, because it is a fairly simple connective tissue that has no blood vessels or nerves.

For over a decade, many physicians believed that the method of lowering blood pressure in patients with systemic hypertension was irrelevant. Now, the data show that angiotensin-converting enzyme inhibitors prolong life more effectively. The explanation is subject to interpretation, but I would argue that angiotensin-converting enzyme inhibitors act at the site of disease that causes elevated blood pressure.

Researchers including myself have discovered new kinds of drugs that could work on the trabecular meshwork and realize the dream of an outflow drug. The present obstacle is one of drug delivery, because this class of drugs does not penetrate the cornea readily as eye drops or, if the agents do, the high concentrations irritate the eye.

The early prototypic drug was ethacrynic acid, on which Duke University holds a patent (all my interest is through the university). This drug and certain now third-generation

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analogs affect the cytoskeleton of outflow-pathway cells.6 Quite simply, cells in the pathway changed shape and thereby allowed more fluid to flow between them. Cell biologists then discovered that rho kinase was one of the master cytoskeletal enzymes. My colleagues and I hypothesized that ethacrynic acid caused the cytoskeleton to contract and thus change the cells’ shape. Much to our surprise, inhibiting the rho kinase enzyme also greatly increased outflow and relaxed the cells.7 Other researchers such as Paul Kaufman, MD, in Madison, Wisconsin, and Benny Geiger, PhD, in Rehovot, Israel, reported similar findings with other agents that relaxed the cells. Importantly, my colleague Vasanth Rao, PhD, informed me that certain statins are rho kinase inhibitors. This revelation led us to hypothesize, not only a possible IOP-lowering role for statins, but also a neuroprotective function—ideas that prompted the recent collaborative study on statins.8

What prompted you to focus on physiology, biochemistry, pharmacology, and cell biology as they relate to glaucoma?

W. Morton Grant, MD, was my mentor while I was a glaucoma research fellow at Harvard. I was stunned then by how little we understood of the physiology, biochemistry, pharmacology, and cell biology of the outflow system and of its relation to glaucoma. Dr. Grant stimulated me to ask questions and to learn how to do specific, controlled experiments to find answers—always with a focus on how these questions related to human beings suffering from a chronic disease for which there were no specific treatments. He encouraged me to study the basic biochemistry of the tissue, and there were many surprises. In the 1970s, some viewed the outflow system purely as a plumbing problem and thought the cells were irrelevant. Moreover, researchers had instilled poisons in experimental eyes to see if they caused glaucoma, but they never did. We discovered that the tissue did not use the oxygen-metabolism pathway much, a finding that explained other investigators’ results with poisons. Jorge Alvarado, MD, and his group at the University of California San Francisco similarly discovered the importance of cell biology. We also observed that, no matter how much pigment we placed into the anterior chamber of a normal, living monkey with a normal outflow pathway, we could not cause chronic pigmentary glaucoma, even though a band of trabecular pigment developed.9 This finding implied the importance of normal cell biology in preventing glaucoma.

How will glaucoma treatment change during the next 15 years?

I predict that, in 5 to 10 years, we will solve the drug delivery problem, and an outflow drug will become available. This agent will restore normal function and revolutionize the treatment of glaucoma. Then, we will be able to home in on the factors in the optic nerve and ganglion cells that cause patients’ varying susceptibility to glaucomatous damage. Right now, IOP is a confounding factor to these studies, because it constantly fluctuates. We do not know how much damage is due to IOP and how much is intrinsic. Perhaps the outflow drug will only need to be injected into the eye twice a year. Just as few people were interested in prostaglandins before the first successful use of these agents, I think the advent of an effective outflow drug will prompt an intense focus of research on the outflow system.

In 10 to 15 years, we will finally have some form of neuroprotective therapy. I hope further research will show that statins are neuroprotective, but then the questions are how and why. Because I suspect there is more than one cause for sickness of the ganglion cells and optic nerve, I think that there will ultimately be several protective therapies.

What advice do you have for the beginning researcher?

I disagree with the many people who assume that only basic scientists are necessary. I call this the trickle-down hypothesis, which holds that someone will eventually relate basic scientists’ findings to glaucoma. That may occasionally happen, but as Dr. Grant maintained, it is the inquisitive physician who can identify the questions needing answers and serve as a bridge from the clinic to the laboratory and back again.10 I believe that basic scientists working in isolation will never cure glaucoma. In an interdisciplinary scientific team, the MD clinician scientist is able to translate science into new understanding of disease.

Young people do not understand how important they are. The field is wide open. As Dr. Grant said, it is amazing what we do not know. I teach our fellows that the glaucoma practice is a clinical laboratory. Specific, focused experiments to test a hypothesis usually yield surprising results and lead to innovation. ■