College of Life Sciences and Agriculture
INSIGHT
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VISION QUEST

An investigation of the biochemical miracle of sight holds promise for those at risk of losing it.

It begins with unexpected moments of clumsiness. You might find it difficult to make out shapes in the darkness. Then your daytime vision deteriorates. You first have trouble seeing out of the corners of your eyes, and later the world becomes a much-reduced circle, like looking down the barrel of a gun. This limited view grows increasingly blurry until everything looks like what has been described as an "unfinished impressionist painting." Eventually, you are completely blind.

You have the most severe form of a condition known as retinitis pigmentosa, and you can no longer do what generally is taken for granted: you have lost the ability to transform light into an image in the mind's eye. UNH Professor of Biochemistry and Molecular Biology Rick Cote has received a $1 million grant from the National Eye Institute to continue an investigation that he hopes will ultimately result in a treatment for this debilitating disease, one that afflicts roughly 1.5 million people worldwide.

"Many visual disorders are caused by abnormal functioning of the retina's photoreceptor cells," says Cote. "In retinitis pigmentosa, these cells gradually degenerate and are not replaced. If we can understand what's happening at the molecular level, we will be better able to intervene in the progression of this disease through therapeutic drugs."

Changing light into sight

Normal vision depends on a thin layer of nerve tissue lining the back of each eye. From *rete*, the Latin for "net," the retina gathers rays of light that have been focused by the lens and cornea and transforms them into electrical impulses through a process called "visual transduction." These impulses travel along the optic nerve to the brain, where they are perceived as images.

Visual transduction is accomplished through the tandem work of photoreceptor cells known as rods and cones. Thickly clustered at the retina's perimeter are more than 100 million bristling rods, which are responsible for peripheral vision, night vision, and the capacity to see in dim light. Color perception, the visual acuity to discern fine detail (such as in reading) and the ability to see in bright light are the business of cones, a much smaller population of cells gathered toward the retina's center.

For those with retinitis pigmentosa (RP), there are many patterns by which rods and cones can fail. From mild tunnel vision to complete blindness, the symptoms that characterize this condition vary so widely among individuals that vision scientists like Cote believe RP is actually a collection of disorders. Yet however they manifest, these retinal malfunctions do have a common bond.

"Retinitis pigmentosa is a genetically inherited condition that passes from one generation to the next," Cote says. "Research has improved our ability to detect its genetic causes, and as a result, genetic counseling can help people when they make decisions about having children."

Identifying the genetic roots of RP is the first step in developing a treatment for the condition. With the help of undergraduates, graduate students, postdocs, and research technicians, Cote has been developing a biochemical model of how rods and cones function in normal eyesight. An understanding of how a healthy retina operates, he says, will illuminate how genetic defects send faulty messages to retinal cells and lead to their progressive degeneration.

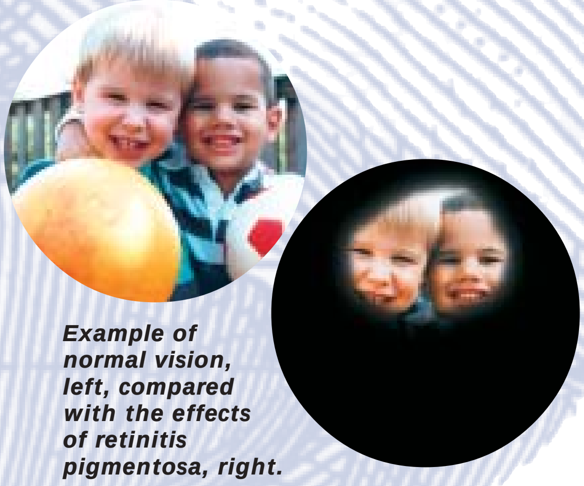
A matter of molecules

Exploring how the retina works its visual alchemy is a bit like opening a series of nested boxes. Understanding this fragile tissue's role in vision requires an analysis of its cells. Teasing out the purpose of rods and cones leads to an investigation of the molecules that allow these cells to perform critical and divergent functions. And the tracing of complex biochemical pathways demands an explanation of how the shape and energy of these molecules change as they do their work.

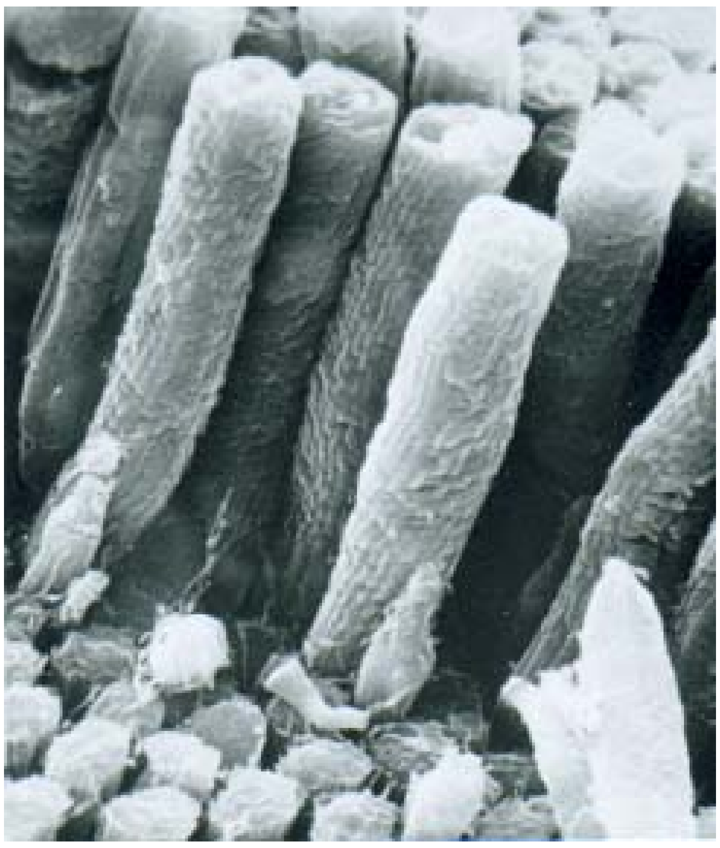
"In rods and cones, there is a class of proteins called 'opsins;' these are the initial point of light absorption," says Cote, as he outlines the molecular steps of visual transduction. "This is followed by the activation of a G protein, transducin, which leads to the activation of the enzyme phosphodiesterase (PDE), which regulates the breakdown of still another molecule, cyclic cGMP."

Understanding how phosphodiesterase works has been a major goal of Cote's research. There are 11 different forms of this enzyme in the body, each of which performs a distinct function. While PDE6 is central to retinal activity, for example, PDE5 moderates the constriction of blood vessels and is the target molecule of the erectile dysfunction drug Viagra.

"Knowing the ways in which all of the PDEs serve a common signaling function will help us understand the general question of how cells talk to each other," says Cote. "Likewise, discerning how retinal PDE6 differs from other phosphodiesterases will help us to design a new generation of drugs that can target one of these enzymes without adverse, unintended effects on the others."



Example of normal vision, left, compared with the effects of retinitis pigmentosa, right.



Bristling rods loom over cones in this scanning electron micrograph. Understanding the biochemical processes at work in photoreceptor cells will help to develop therapeutic treatments that stop or slow down the progression of disorders such as retinitis pigmentosa, night-blindness, and macular degeneration.

Filling in the big picture

From a woodland's fading twilight to the near-blinding midday sun on a snowy mountaintop, our vision functions over a remarkable range of ambient light levels. This ability, known as light adaptation, is accomplished through biochemical signaling pathways in photoreceptor cells. To date, much of Cote's work has centered on one such pathway, the activation of phosphodiesterase in rods. But because the biochemical activity of rods can tell us only about vision at low light intensities—bright lights easily saturate rod cells—Cote is turning to a new focus.

"Cones are responsible for vision in bright light, but we know little about them, in part because they are much less abundant than rods, and are harder to purify," he says. Along with a team of collaborators, at UNH and around the world, Cote hopes to unravel the elusive mysteries of cone vision and bring greater clarity to the process of light adaptation.

Such an understanding promises to bring us closer to the light at the end of a long, dark tunnel—not only for those with the potential to develop retinitis pigmentosa, but for people at risk for rod-cone dystrophy, night-blindness, macular degeneration, and other disorders tied to defects in the normal functioning of the retina.