climate change, and the indirect and synergistic impacts of these threats. What might be more surprising is that even micro-level case studies struggle to attribute wildlife declines to a specific cause. Three new studies of wildlife declines in Australia’s protected areas demonstrate this point.

In a detailed multiyear study in Kakadu National Park, Woinarski et al. (13) systematically surveyed small mammals and observed a 63% decline in species richness and a 75% decline in abundance from 1996 to 2009. Importantly, the researchers suggested that causes of the declines were species-specific and may have involved the individual or combined effects of changes in fire frequency and habitat structure, increases in invasive predators (feral cats and cane toads), and other factors that were not easy to measure. Fire and invasive predators also feature as likely culprits in new research by Firth et al. (14) on the extinction of the brush-tailed rabbit-rat in Australia’s Garig Gunak Barlu National Park. Here, the authors experimentally determined that dry-season fires significantly reduced wildlife survival, but they also observed population declines in their unburned control areas and concluded that additional threats were at work. In contrast to these studies, Ford et al. (15) found that invasive species and fire played no major role in the decline of the brown treecreeper and hooded robin in New South Wales, Australia, but did observe powerful, lagged effects of isolation due to habitat loss and fragmentation over the past 100 years. Together, these studies emphasize the site- and species-specific drivers of wildlife declines. They also emphasize that the factors responsible for endangering a species may be distinct from the challenges experienced by dwindling populations of survivors. This point is illustrated tragically by the recent extinction of mountain caribou in Canada’s Banff National Park; years of population decline from habitat loss, isolation, and apparent competition with moose ended with the death of the last known individual in an avalanche (16).

Research over the past 20 years shows that wildlife persistence is often positively associated with the size, connectedness, and remoteness of protected areas and the intactness of surrounding ecosystems (17). Beyond this, though, there are few obvious patterns or golden rules for predicting wildlife declines in protected areas. The lesson from this research, however, is not that we must surrender to the indecipherable complexity of modern declines and resign ourselves to inaction. Instead, we need to move away from broad generalizations and toward species- and community-specific approaches to conservation. A critical first step is a renewed commitment to wildlife monitoring in protected areas. The nearly exponential growth rate of protected areas since 1903 has greatly outpaced the allocation of resources for monitoring. Governments have used debt relief, foreign aid, direct payments, and other methods to incentivize the creation of protected areas in developing regions. Yet, there exist strikingly few incentives or resources for monitoring the fate of biodiversity in protected areas of the developing or developed world. While conservation science has made headway in quantifying the effectiveness of protected areas, our heavy reliance on habitat cover trends, expert opinion, and questionnaire does not allow us to fully understand or affect the dynamics of wildlife decline. Intensive, long-term monitoring is essential to gaining empirical knowledge of synergies among threats, the role of indirect effects, and other questions critical to minimizing species loss in protected areas.

References and Notes
3. These species are present in Yellowstone National Park today due to reintroduction and recolonization.
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NEUROSCIENCE

Seeing the Light of Day

A potential gene therapy approach could restore some vision to patients with retinitis pigmentosa.

H
uman beings are highly dependent on vision. It is our most well-developed and cherished sense, giving us color vision with high acuity during the day as well as excellent sensitivity at night. Vision begins with light reception by specialized cells in the retina, a thin sheet of neural tissue that lines the inside of the eyeball (1). Rod photoreceptors provide for sensitivity in dim light, whereas cone photoreceptors provide for color vision in bright light. Unfortunately, photoreceptors are very sensitive to genetic insults. Mutations in more than 200 genes can lead to blindness, more than 40 of which lead to the disease retinitis pigmentosa (2, 3). This disorder typically is due to a mutation in a gene expressed only in rods, and thus individuals with retinitis pigmentosa mutations are often born night-blind. Between ages 20 and 60, cone-mediated vision deteriorates (4), leading to total blindness. The poorly functioning cones in retinitis pigmentosa are the target of a potential gene therapy approach reported by Busskamp et al. on page 413 of this issue (5).

When stimulated, most neurons are depolarized and release more neurotransmitter. Photoreceptors are unusual, becoming hyperpolarized when stimulated (by light). Thus, for a signal to mimic light, the signal must hyperpolarize a photoreceptor. Halorhodopsin, a light-activated chloride pump of archaeabacteria (6), does just that. Busskamp et al. delivered halorhodopsin [using an adeno-associated vector (AAV)] to cone photoreceptors in two mouse models of retinitis pigmentosa, hoping to bypass the need for the normal light sensor (opsin) in cones and the normal phototransduction process. Indeed, the authors detected light-induced electrical currents in the vector-infected photoreceptor cells, not unlike those measured in normal cones in which light stimulates cone opsin. In a normal retina, neurons that receive signals from photoreceptors extract patterns of interest, such as those that convey the direction of motion.
Future therapy? It may be possible for a viral vector to deliver halorhodopsin to retinal cone cells of a patient with retinitis pigmentosa. Upon light stimulation, halorhodopsin pumps chloride ions into the cell, thereby hyperpolarizing it. This mimics the normal light response of photoreceptors and changes the rate of neurotransmitter (glutamate) release. The glutamate signal is processed into information (by inner neurons) and transmitted to the brain (by ganglion cells). To provide halorhodopsin with the appropriate stimulatory light, special eyeglasses would use a camera to detect light, adjusting to a wide range of intensities. The camera signals to LEDs on the inner surface of the eyeglasses, which then emit light of the proper wavelength for stimulation of halorhodopsin in cone cells.

or changes in light intensity. These signals are then sent to the brain by ganglion cells. By recording electrical activity from the ganglion cells of retinas expressing halorhodopsin, Busskamp et al. show that the neuronal circuitry of the retina is functional. Not only did the cones and the ganglion cells in the retinitis pigmentosa mice respond to halorhodopsin-derived signals, but these signals enabled the mice to see, distinguishing dark from light and detecting the direction of motion.

The hope is that AAV-halorhodopsin will be nontoxic and effective enough within the normal range of light intensities to prolong vision in humans with retinitis pigmentosa, and perhaps other genetic diseases as well. The first experiments toward this goal also were reported by Busskamp et al. By infecting cultured human retinas with the vector, they demonstrate expression and function of halorhodopsin in human cone photoreceptors. The next step will be to test AAV-halorhodopsin for toxicity in nonhuman primates. So far, toxicity in mice has not been detected. Busskamp et al. engineered the viral vector to use a photoreceptor-specific promoter to express halorhodopsin, which limits the potential for toxicity. AAV vectors have proved to be stable and free of side effects when used to infect the human eye (7, 8). In fact, children with another form of genetic blindness, Leber’s congenital amaurosis, have been successfully treated by gene therapy with AAV (9).

AAV-halorhodopsin should allow cones to function until they eventually die from the disease. The cause(s) of death are not clear, but may include autophagy, which occurs in response to starvation (10). Cones also suffer from oxidation due to the high oxygen tension that occurs when rods, the most abundant photoreceptors, die from the effects of the retinitis pigmentosa mutation (11). Growth factors, which may or may not be required for cone survival, can slow the progression of photoreceptor death when added using several different approaches (12, 13). Thus, it may be possible to treat cones with a dual gene therapy—a viral vector that delivers a gene to combat the underlying cause of death, along with the halorhodopsin gene. Alternatively, a combination therapy of antioxidants, and/or growth factors, and AAV-halorhodopsin might prolong cone survival and function.

How will humans treated with this gene therapy perceive the halorhodopsin-derived signals? Cones have opsins that are tuned to different wavelengths of light (red, green, and blue). Neuronal circuitry in the retina compares the relative signals from these different types of cones, and ultimately the brain interprets these differences as particular colors. Halorhodopsin produces a signal in each type of cone without allowing for discrimination of different wavelengths. Thus, a person receiving this gene therapy will likely experience a monochromatic view of the world. If this still serves for useful vision, as it did in the mice, it will be good news.

There is one additional aspect of this strategy to be considered. Human vision is normally active over a very wide range of light intensities (up to 10 logarithmic units) because of multiple mechanisms within the retina and eye (1). The amount of light it takes to activate halorhodopsin is high, approximately the amount one would encounter on the beach during the day, and is limited to a range of about three orders of magnitude (5, 6). To amplify low light intensities and increase the dynamic range of visual responses, eyeglasses with light-emitting diodes (LEDs) are being developed that emit light of the optimum wavelength for activating halorhodopsin (14). These eyeglasses use a camera pointed out at the world (see the figure), which can adjust to a wide range of light intensities, just as a video camera can be used outside or indoors. After light detection, the camera relays signals to a sheet of micrometer-sized LEDs on the inner layer of the eyeglasses. The LEDs then emit light of the proper wavelength to stimulate halorhodopsin expressed in photoreceptors. Perhaps this ingenious device, coupled with the right gene therapy, will allow a person with retinitis pigmentosa to retain vision for a prolonged period of time.

References
2. www.sph.uth.tmc.edu/Retnet
5. V. Busskamp et al., Science 329, 413 (2010); published online 24 June 2010 (10.1126/science.1190897).