Regaining the Rainbow

Genetic intervention cures color blindness in monkeys

BY CHRISTOF KOCH

Men are more often color-blind because two genes that enable the eye to absorb light sit on the X chromosome. Men have only one X; women have a backup.

THERE IS AMPLE EVIDENCE that men and women think, express themselves and even experience emotions differently (for more details, read on through this issue). But in the area of sensory perception, psychologists are hard-pressed to identify major discrepancies. By and large, the way the two genders experience the sounds, sights and smells of life is quite similar. The most striking exception may be found, at least for some, in the perception of colors.

Seeing in color is a complex process, as you may remember from your school days. It starts with the delicate lining of the eyes, a structure called the retina. Retinal tissue contains light-sensitive cells that absorb wavelengths in the visible spectrum and convert them into electrical signals. The brain interprets this information as the riot of colors we consciously experience. The retinal cells called cones come in three varieties. The S-type cone is maximally sensitive to light in the short-wavelength (blue) part of the visible spectrum, the M-type cone responds best to medium wavelengths, and the L-type to long, reddish wavelengths. People with normal color vision are known as trichromats because they possess these three kinds of photosensitive cone cells.

About 8 percent of men, but fewer than 1 percent of women, have impoverished color vision, typically because they lack the gene for either the L- or the M-type photopigment. While their vision is normal in every other way, they suffer from what is often called red-green color blindness. Depending on the specific genetic omission involved, such people—who are known as dichromats because they have only two types of cone cells—are unable to distinguish between violet, lavender and purple or between red, orange, yellow and green.

It's not a tremendous handicap, but it can make traffic lights—especially horizontal ones—as well as warning lights that flash either yellow or red hard to decode. And a lack of sensitivity to reddish hues makes it almost impossible for a dichromat to detect the onset of sunburn. (The photographs on the opposite page show the sickly-looking hue of skin as seen through color-blind eyes.)

The reason color blindness is so much more common in boys and men is that the two genes for the L- and M-type photopigments—the substances in cone cells that absorb light—are carried on the X chromosome. A girl who inherits one defective copy of such a gene from her parents has a backup on her other X chromosome. Because men have only one X chromosome (their paired sex chromosome is a Y), they lose out. Interestingly, also thanks to the vagaries of genetics, some women are endowed with four kinds of photosensitive cones instead of the standard three. Theoretically, these so-called tetrachromats can identify subtleties of shading that are indistinguishable to the rest of us; however, this phenomenon has been hard to confirm experimentally.

Color Correction

Unlike humans, most mammals possess just two kinds of retinal cones. Thus, mice, cats and dogs see the world much the way a red-green color-blind person does, making them ideal experimental subjects. A few years ago scientists at the Johns Hopkins School of Medicine inserted the gene for the human L-type photopigment into mice. After several generations of breeding, the mice responded to the extra hue information. They had changed from dichromats to trichromats—a remarkable feat of bioengineering. The experiment also showed that mouse brains are flexible enough to receive and make use of the additional wavelength information.

An even more ambitious experiment, extending over a decade, came recently to fruition. It was conducted by the husband-and-wife team of Jay Neitz and Maureen Neitz, both professors at the

CHRISTOF KOCH (*Koch*); OLEKSIY MAKSYMENKO *All Canada Photos/Corbis (rainbow eye)*

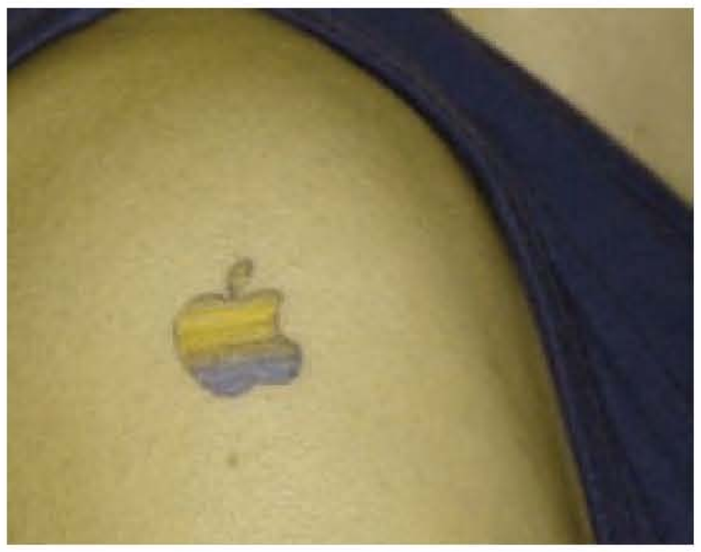
We could potentially **extend human vision** into the ultraviolet or infrared: the superhero spectrum.

University of Washington School of Medicine, and their collaborators. The work involved squirrel monkeys, a species indigenous to Central and South America. Among these primates, most females are trichromats, but the males are dichromats, possessing only the S- and M-type photopigments. Accordingly, it is the females that lead troops of monkeys to search for ripe fruits among the foliage, a quest that requires superior color discrimination skills.

The Neitzes wondered: Could gene therapy "cure" the male monkeys' color blindness? To find out, the biologists developed a way to incorporate the gene for the human L-type photopigment into a small virus known as adeno-associated virus. Next they injected tens of trillions of viral particles into the monkeys' eyes. Twenty weeks later up to one third of the M-type cones in the animals' retinas had begun to express the L-type photopigment. In other words, the monkeys now had not two but three cone types: in addition to their original S-type and M-type cones, they had new M-type cones whose sensitivity had shifted toward the long-wavelength part of the spectrum.

The million-dollar question was whether the rest of the animals' central nervous system could reprogram itself to make use of this additional information. Using a computer-administered color test, the Neitzes demonstrated that the treated monkeys, like the mice from the earlier experiment, did indeed discriminate among colors.

The monkeys' new color awareness emerged as soon as the photopigments were expressed in their retinas. The lack of delay suggests that preexisting retinal and cortical circuitry can incorporate the additional information; no time-consuming rewiring was necessary. It also suggests how the evolutionary transition from two- to three-cone color vision might have come about.



Two views of the author's right deltoid: A regular one (*left*), and a manipulated one (*right*) that suggests how it would look to a color-blind person who doesn't see reddish wavelengths.

From Monkeys to People

Two years after the Neitzes' experiment their monkeys' color vision remains transformed. Being the careful scientists they are, they do not take a stand on whether or not the monkeys see novel reddish hues. Yet I find no principled reason to deny it. The retinal machinery for trichromacy is present, and the monkeys' behavior indicates that they experience these hues. Within a few years electrophysiological and functional imaging experiments will inform us whether the animals show increased processing in the regions of visual cortex dedicated to color perception. I would bet 100 to one that they do.

The virus used in this experiment is safe—it doesn't replicate by itself, doesn't cause disease and triggers only a mild immune response—and it has been approved for gene therapy in humans. So this technique could be adapted to help color-blind people see normally. The condition affects many millions in the U.S. alone. Provided that the risk-to-benefit ratio of gene therapy can be improved significantly, a potential cure could have a dramatic impact on the sensibilities of a large slice of humankind.

Jay Neitz believes that this operation will someday become as safe as refractive surgery such as Lasek. Methods such as the one the Neitzes have pioneered, as well as the optogenetic techniques discussed in my last column [see "Playing the Body Electric," March/April 2010] may well, soon enough, make the (color)-blind see again.

Of course, there is little reason to stop there. Why not enhance visual experience to give the more adventuresome among us tetrachromacy? Or extend the window of visibility up into the ultraviolet or down into the infrared for superherolike vision? Thanks to cutting-edge molecular biology, we can see our way into a transhuman future. **M**

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(Further Reading)

- **Emergence of Novel Color Vision in Mice Engineered to Express a Human Cone Photopigment.** G. H. Jacobs, G. A. Williams, H. Cahill and J. Nathans in *Science,* Vol. 315, pages 1723–1725; March 2007.
- **Gene Therapy for Red-Green Colour Blindness in Adult Primates.** K. Mancuso, W. W. Hauswirth, Q. Li, T. B. Connor, J. A. Kuchenbecker, M. C. Mauck, J. Neitz and M. Neitz in *Nature,* Vol. 461, pages 784–787; October 2009.
- The Neitz Laboratory Web site: **www.neitzvision.com**

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