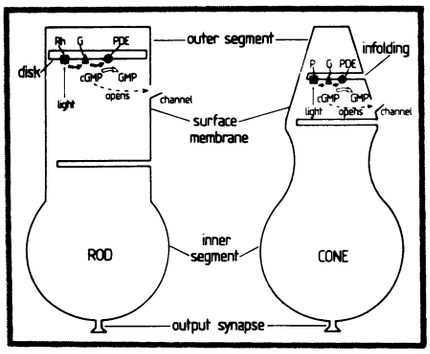
# Turnabout in Vision: Messenger Unmasked

A small molecule called cyclic GMP has now been recognized by scientists as the crucial messenger chemical in both types of cells that sense light in animals' eyes. Light striking the retina of the eye triggers in these photoreceptor cells a cascade of molecular events that eventually generates the electrical signals essential for vision. For almost 15 years, scientists had favored a hypothetical description of this cascade in which light released calcium from storage within a photoreceptor cell, and this "messenger" calcium interacted with channels in the outer membrane to produce the electrical signal.

The recent direct evidence that the internal messenger is cyclic GMP rather than calcium ions comes out of experiments with a powerful, relatively new technique called "patch clamping" (SN: 11/7/81, p. 295). Rather than dealing with all the complexities of a cell, the patch-clamp technique isolates a small circular segment of outer membrane from a photoreceptor cell — a rod or a cone. Solutions containing calcium ions or cyclic GMP are applied to each side of this membrane patch, and channel activity is monitored.

Such experiments demonstrate that exposing the inner surface of the rod cell membrane to cyclic GMP rapidly causes the channels to open, but calcium does not have this effect. These results were reported earlier this year by several independent research teams led by Evgeniy E. Fesenko at the USSR Academy of Sciences in Pushchino, King-Wai Yau at the University of Texas Medical Branch in Galveston, T.D. Lamb at the University of Cambridge in England, and W.H. Cobbs and E.N. Pugh Jr. at the University of Pennsylvania in Philadelphia.

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*The early steps in light reception: Light is absorbed by rhodopsin (Rh) located in the disk membrane of rods and by other pigments (P) on the infolded membrane of cones. In each case the activated rhodopsin turns on a GTP-binding protein (G), which activates an enzyme called phosphodiesterase (PDE). This enzyme breaks down cyclic GMP. Because cyclic GMP keeps the surface membrane channels open, this light-activated cascade acts to close these channels. The channel closing interrupts an electrical current and decreases the neurotransmitter released from the synapse to other retinal cells.*

Cones have always been more difficult than rods to use in experiments, and so have remained more mysterious. The geometry of a rod cell demands that there be some messenger substance; the light-sensing molecules, rhodopsins, sit in membrane disks that are not continuous with the outer membrane containing the ion channels responsible for the electrical signal. But in cones, the light-sensing molecules are located on deep infoldings of the outer membrane — so a messenger chemical might not be required.

In the Sept. 5 NATURE, however, two research groups — those of Yau and of Cobbs and Pugh — report that cones of catfish and of larval tiger salamander do use cyclic GMP as a messenger. This finding was somewhat unexpected because biochemical experiments had suggested that light modulates the level not of cyclic GMP but of the related molecule, cyclic AMP.

In both rods and cones the action of cyclic GMP is a biochemical novelty. Scientists had previously observed that in other cells, cyclic GMP mediates the activity of membrane channels via an enzyme reaction, called phosphorylation. But in the photoreceptor cells the cyclic GMP acts directly on the channels, allowing a faster response time. Now the scientists are asking whether the same mechanism exists in other cells.

*—J.A. Miller*

## Smoking and cancer: Value in paradox

An epidemiologic study of endometrial cancer shows that women who smoke have a lower incidence of this cancer of the lining of the uterus than do nonsmoking women. That doesn't mean, say the researchers, that women should take up the habit — the specter of smoking-related diseases greatly overshadows the cancer-protective benefit. The value of the study, they say, is in prompting further investigation into what causes the protective effect to see if it can be exploited for prevention.

Samuel M. Lesko of Boston University and researchers from five other U.S. institutions looked at 510 women 30 to 69 years old hospitalized for endometrial cancer and 727 women in the same age range hospitalized with cancers unrelated to cigarette smoking. Current smokers were at 0.7 times the risk of endometrial cancer as nonsmokers, the researchers report in the Sept. 5 NEW ENGLAND JOURNAL OF MEDICINE. The more extreme the habit, the greater the "benefit" — women currently smoking more than 25 cigarettes a day were at half the risk of women who had never smoked. The effect was seen primarily among postmenopausal women.

"The present findings do not have direct public health importance since cigarettes, overall, have serious deleterious effects," note the researchers. And in an accompanying commentary, Noel S. Weiss of the University of Washington in Seattle observes that while smoking will each year spare 30 of 100,000 women smokers from getting endometrial cancer and six from dying of it, the habit kills about 30 times that many women through other diseases.

The mystery here is how cigarettes exert a beneficial effect. The researchers and Weiss suggest that the common denominator between smoking and a reduced risk of endometrial cancer is the hormone estrogen. Other studies, they note, have shown that cigarette smoking lowers estrogen levels in the body, and high levels of estrogen have been linked to endometrial cancer.

The estrogen connection raises its own question: How and when do estrogen levels play a role? Lesko and his colleagues point to a 1982 study led by Brian MacMahon at Harvard University showing that during one part of the menstrual cycle women smokers had lower estrogen levels than nonsmokers. But if the cigarette benefit had been mediated by its menstrual cycle effect, counters Weiss, the Boston University study would have shown a substantial risk reduction in premenopausal women. "Just about everything we know suggests that estrogen has a very rapid effect on endometrial cancer," he says. Endometrial cancer incidence goes up within a couple of years in women taking estrogen to reduce the side effects of menopause and goes down within a couple of years of stopping, he notes.

Weiss suspects a counterplay between estrogen and progesterone, another hormone involved in the female reproductive system, as a key factor in endometrial cancer. In premenopausal women progesterone balances estrogen, so the effect of smoking wouldn't be expected to play a role. After menopause, while progesterone production halts, some estrogen is still produced.

*—J. Silberner*