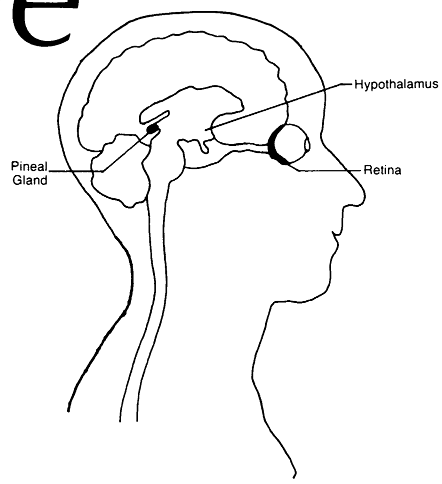
# Eye to (Third) Eye




## Scientists are taking advantage of unexpected similarities between the eye's retina and the brain's pineal gland

By JULIE ANN MILLER

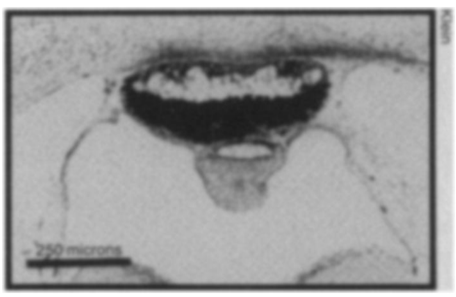
From daily light-dark cycles to detailed visual configurations, patterns of illumination in the environment have profound effects on animals. The retina and the pineal gland are the organs primarily responsible for the body's recognition and sophisticated processing of external light. Until recently these two organs in mammals seemed to have little else in common and were consequently studied by separate groups of scientists. But a new alliance of researchers is now exploring striking similarities that are speeding research efforts in both fields. Their findings suggest that the pineal gland was the evolutionary precursor to the modern eye.

Only the retina senses light directly. It produces nerve signals that travel to the brain. In contrast, the pineal gland uses nerve signals from the brain to coordinate a daily. circadian rhythm of hormone release. Melatonin, the hormone produced by the pineal, influences animals' breeding cycles, migrations, changes in coat color, growth, loss of antlers and other physical and behavioral characteristics that vary seasonally. There is also speculation that melatonin in humans strongly influences mood.

The new alliance between researchers working on these apparently disparate organs began several years ago with the observation of a daily rhythm in the retina. While it turned out that the retinal rhythm is independent of the pineal gland, once the groups of scientists began working together they discovered surprising similarities between the two organs, including the presence of melatonin in the retina as well as in the pineal gland.

"It was like finding a relative you didn't know you had," says Paul O'Brien of the National Eye Institute in Bethesda, Md. "We are eager to know just how much we have in common." O'Brien and David Klein, who studies the pineal gland at the National Institute of Child Health and Human Development in Bethesda, organized the first symposium on "pineal-retinal relationships," in Sarasota, Fla., last spring.

A comparison of the anatomy, physiology and biochemistry of the pineal gland and the retina across a wide range of animal species indicates that the organs share evolutionary and developmental paths. Perhaps the most striking evidence of this link is the "third eye," first described in a lizard more than a century ago. In the Western fence lizard, for example, this "eye" is a yellow-white spot that sits in a 1-millimeter opening between the skull bones on the top of the head. This "eye" is an extension of the pineal gland, but like other eyes, it contains a retina, lens and cornea. A variety of other species, including lizards, frogs and lampreys, have more or less elaborate pineal eyes.




*Pineal glands lack the complex stratified structure characteristic of retinas. In this lamprey pineal gland, the sensory cells (dark layer) are densely packed. Some pineal "eyes" also have a lens and cornea.*

Although the pineal eye resembles other eyes, and so seems likely to sense light, the animals show no obvious behavioral response to light falling on that organ. In the 1960s scientists demonstrated an electrical response from pineal eyes when they were illuminated. These eyes do not focus, so they only sense ambient light rather than the detailed patterns perceived by the retina.

While most animal species do not have a true pineal eye, the pineal gland is sensitive to light in many nonmammalian species, including birds, fish, reptiles and amphibians. The detailed cellular anatomy of the nonmammalian pineal gland resembles to varying degrees aspects of the retina.

In the retina, light is sensed by photoreceptor cells called rods and cones, which have characteristic stacks of light-sensitive membranes. Pineal glands of birds, fish, amphibians and reptiles have similar cells, although they tend to be more rudimentary and more randomly oriented than in the retina. There is even a suggestion that some cells in mammalian embryonic pineal glands resemble photoreceptor cells.

The pineal gland does not, however, have the complex layered structure that serves the eye in processing information. "The pineal looks like a blob, compared to the retina," O'Brien says. Whereas the retina has five distinct types of nerve cells, the pineal seems to have, at most, only receptor and output (ganglion) cells.

The most striking discovery of the recent communication and collaboration is that, in addition to melatonin's presence in the retina, proteins that had been thought to be unique to the retina are also present in the pineal gland. A series of proteins involved in the processing of light in the retina (SN: 9/14/85, p. 164) includes rhodopsin, the pigment that absorbs light; GTP-binding protein, or transducin; an enzyme called rhodopsin kinase; another called S-antigen; and a retinoid- (vitamin A-) binding protein.

Because each retina is 10 times larger than a pineal gland and the chemicals are concentrated in cell segments that are easy for scientists to isolate, researchers have been able to purify each of these retinal proteins, produce antibodies that bind to it specifically and then use the antibodies to detect the protein in other organs.

"We can use the retina as a factory for

making chemicals to study the pineal," Klein says.

This work has provided evidence that each of these proteins, or a near relative, is present in pineal glands of some species but not in other body tissues. A rhodopsin-like protein and a transducin-like protein have been observed in the light-sensitive pineal glands of birds, fish, amphibians, reptiles and lampreys, but not in the pineal glands of mammals.

In some mammals, as well as other animals, S-antigen, rhodopsin kinase and retinoid-binding protein have been located in pineal glands. In one experiment, S-antigen caused an inflammation of the pineal gland similar to the sometimes blinding disease of the retina known as uveitis. The retinal condition is thought to be caused by natural antibodies, especially antibodies to S-antigen.

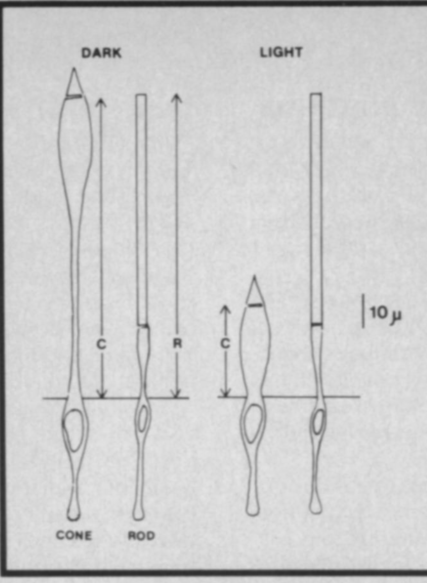
"Our job as physiological chemists is to figure out what these retinal proteins are doing in the pineal gland," says Klein. He suggests that a rhodopsin-like molecule in the pineal gland might be a membrane receptor that responds not to light but to a neurotransmitter chemical released by brain cells. The binding of that neurotransmitter would initiate a cascade of events employing the same components as the retinal response to light.

Not only does the pineal gland resemble the retina, but the retina has come to be credited with properties formerly associated only with the pineal gland. The work that originally brought together retina and pineal gland researchers at the National Institutes of Health was a study of the retinal phenomenon called "disk shedding." The long, cylindrical photoreceptors called rods contain a stack of flattened sacs whose membranes contain rhodopsin. These disks are produced near the cell body and gradually advance within the rod to the outermost tip. The tip repeatedly breaks off and is destroyed by nearby cleanup cells. In mammals, about 10 percent of the stacked disks of each photoreceptor are shed each day.

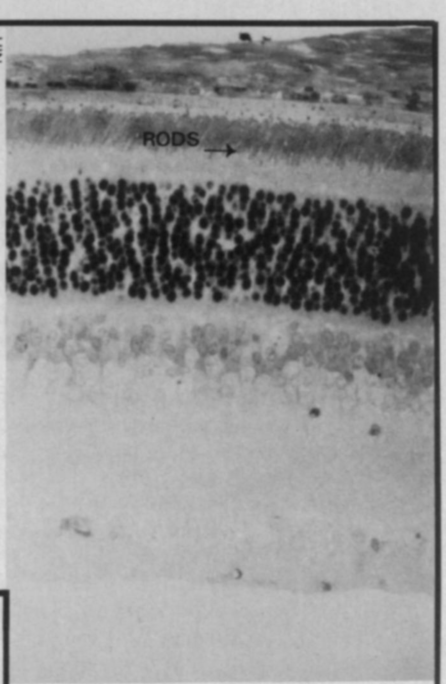
Disk shedding in the retina occurs on a daily cycle. In rats maintained on a light-dark cycle, there is a burst of shedding soon after the onset of light, even when the pineal gland has been removed.

"We realized we had another source of a biological clock. It is located in the retina, but set by a mechanism involving the brain," says O'Brien. "In working out the details, the retina people have benefited from all the information amassed on pineal gland rhythms over the last 10 years."

The research demonstrated that the retina, like the pineal, produces melatonin in a daily rhythm. The retina employs the same enzymes for melatonin synthesis as does the pineal gland. Activity of one of the enzymes of the melatonin synthetic pathway has been shown in an amphibian to




Beth Burnside et al.




NIH

have peak activity at night, when the most melatonin is produced. The retina produces less than 10 percent of the body's melatonin, and probably does not influence any other tissue, O'Brien says.

The timekeeping activity of the retina extends to another phenomenon. In fish, the photoreceptor cells called cones move within the retina on a daily cycle. They elongate during the night and contract during the day. Melatonin mimics darkness in these retinomotor activities.

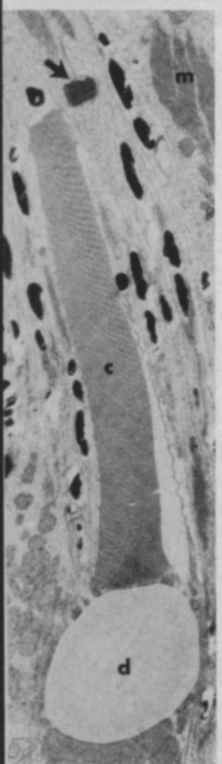
The action of the melatonin produced both by the retina and by the pineal gland appears to involve a neurotransmitter called dopamine. This neurotransmitter affects processes in the retina and in other tissues throughout the body.

"It is now my view that the pineal gland — the so-called third eye — was the first eye," Klein says. "The most primitive visual organ was a single 'eye' that had only to convert light into chemicals." Later in evolution, he says, this organ produced nerve signals as well as a hormonal response. Eventually, the retina evolved and in mammals each organ became extremely specialized.

"The [mammalian] pineal has dropped out of the business of collecting light," O'Brien says. It concentrates on hormone, rather than nerve signal, production. This division of labor allows increased flexibility. In fact, when there is no light-dark cycle, the pineal can entrain an animal's rhythms to daily fluctuation in temperature or in noise.

The specialized retina produces far less melatonin than does the pineal gland, but it has fine-tuned its light-sensing operation. Although the pineal regulates the circadian rhythm of many body functions, the retina has retained control over the daily rhythms of its own functions.

"Our most optimistic hope," Klein says, "is that we may someday use the pineal gland as a source of genetic spare parts to treat diseases of the retina." □




(2) R. W. Young © 1977 Academic Press, Inc.

*Retina rhythms: In a fish eye, photoreceptor cones (C), but not rods (R), elongate at night and contract during the day (diagram, upper left). In another daily cycle of the retina (left, X13,000), the tips of lizard photoreceptor cells break off. The tip is then engulfed by a cleanup cell (arrow, lower left, X4,500). The retina (above) has a striking structure, with the light-absorbing outer segments of photoreceptor cells in one layer (rods) and in other layers the retina cells that begin the processing of visual information.*