entire stand is often a single individual.

As predicted, the fires were a good tonic for aspen, triggering intense sprouting from roots and something "almost never seen in the wild," says Romme: young aspens growing from seeds. But the shoots are a favorite food of elk, and every winter since the fires, elk have zeroed in on aspen shoots sticking out of the snow. As a result, says Romme, the fires have actually "hastened the demise of some stands." The story is not over, however: Roots continue to send up shoots, and if the trees are able to mature, aspen "could still become a key component of succession," Romme says. "We should have interesting results in a couple of years."

Scientists have also tried to put the fires into a historical context. After studying more than 50 fire-related debris flows—landslides that sweep through denuded land and can travel up to 100 kilometers an hour—that have occurred in Yellowstone over the past 3500 years, geologist Grant Meyer of Middlebury College in Vermont says he has found that "big fires ... are strongly controlled by climate." Such flows were much more common from A.D. 900 to 1300—known as the "Medieval Warm Period"—than during the period from 1300 to 1900, called the "Little Ice Age," Meyer says.

Oregon's Whitlock and grad student Sarah Millspaugh have come to similar conclusions after studying charcoal-laced sediments at the bottom of Yellowstone lakes. These studies on past fires have prompted Whitlock to gaze into the future to try to forecast how climate change might alter vegetation patterns and, perhaps, fire frequency and severity. Whitlock, along with Patrick Bartlein and Sarah Shafer, has created computer models to predict the changes in species distributions in the Yellowstone region that may occur in response to global changes from a doubling of atmospheric CO_2. According to results reported in *Conservation Biology* in June 1997, the team predicts that warmer, wetter winters could help alter the ranges of various species in the U.S. Northwest, causing larch, scrub oak, and other trees not now found in Yellowstone to spread into the park. This new landscape could be vulnerable to more frequent, possibly smaller fires, Whitlock says.

The prospect that the Yellowstone ecosystem is poised for a makeover is spurring fire ecologists and colleagues from other disciplines to try to organize a lasting Yellowstone research program affiliated with the National Science Foundation's network of Long-Term Ecological Research sites. But the fire policy won't change, say park officials and researchers. "If our mandate is to manage Yellowstone for future generations as an unhindered ecosystem, then putting out fires is counter to that mandate," says Despain. "The fires have brought home the inevitability of change," adds Duke's Christensen, "and the process of renewal that accompanies it."

–Richard Stone

DEVELOPMENTAL BIOLOGY

One-Eyed Animals Implicate Cholesterol in Development

In ancient times, Homer depicted the one-eyed Cyclops as a terrifying and mysterious monster. Today we recognize infants born with cyclopia—marked by a single large eye—as victims of a defect that derails the normal development of the brain and face. But just how this developmental pathway ordinarily works has been far more mysterious than the ways of Homer's gods and heroes. Now biologists are dissecting it. At its heart, they are glimpsing a familiar molecule, cholesterol, in an entirely new role.

Cyclopia and milder forms of the same developmental disorder result from a failure of the embryonic forebrain to subdivide properly. Defective genes can disrupt this process in people and animals, but so can certain toxins, some of them found in wild plants, and their workings are giving scientists new insights into the developmental pathway. As Philip Beachy, a molecular biologist at The Johns Hopkins University School of Medicine in Baltimore, and his colleagues report on page 1603, these toxins make the cells unable to respond to a critical developmental signal, perhaps because they interfere with the normal traffic of cholesterol within cells. A second group, at the University of Washington, Seattle, has carried out similar experiments, to be published in an upcoming issue of *Development*.

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Very noxious weed. *Veratrum californicum*, or corn lily, can induce developmental defects in sheep.

The idea that a disruption in cholesterol transport may prevent embryonic cells from heeding the signal—a protein called Sonic hedgehog—comes on the heels of earlier work by the Beachy group showing that cholesterol also plays a role in activating the signal in the first place. Together, the findings provide some of the first clear evidence that cholesterol, long known as a structural component of cell membranes and as the raw material that the body converts into steroid hormones and bile acids, can also influence the signaling paths that guide development. "Everyone knew that cholesterol was important," says Yvonne Lange, a cell biologist at Rush-Presbyterian-St. Luke's Medical Center in Chicago. "But that it could act on a [developmental] signaling process was entirely unanticipated. This work opens up a whole new role for cholesterol and raises a lot of interesting questions."

Among the most tantalizing: whether a mother's diet and cholesterol metabolism play some role in determining the severity of the birth defect that, in its most extreme form, manifests itself as cyclopia. One in 16,000 babies is born with some form of the defect, technically known as holoprosencephaly (HPE), says Maximilian Muenke, a human geneticist at the National Human Genome Research Institute in Bethesda, Maryland, and the Children's Hospital of Philadelphia. Early in pregnancy, before nature exerts quality control and flawed embryos are spontaneously aborted, the rate is much higher: one in 250. People with the mildest form of the disorder have signs as minor as a single upper front incisor; severe cases are marked by one eye in the middle of the face, below a protruding nasal structure, and serious brain abnormalities. Infants with full-blown cyclopia die soon after birth.

In 1996, Beachy's group found that HPE-like symptoms, including cyclopia, develop in mouse embryos that lack a normal *Sonic hedgehog* (*Shh*) gene. *Shh* is the vertebrate counterpart of a fruit fly gene called *hedgehog* (*hh*), which instructs the nervous system to develop properly. The same gene is at fault in some human cases, Muenke and his colleagues Stephen Scherer and Lap-Chee Tsui at the Hospital for Sick Children in Toronto soon showed. Muenke says he has also found that mutations in other genes affecting the Shh signal can cause HPE. But many cases of HPE have not been traced to specific genetic lesions, opening a possible role for environmental factors.

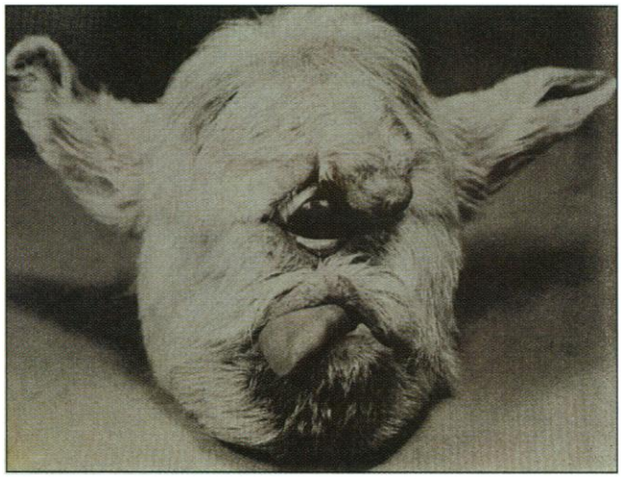
At least in animals, toxins that interfere

with cholesterol metabolism can cause similar abnormalities. The first solid clue that cholesterol might play a role in development came 2 years ago, when Beachy and his colleagues discovered in test tube experiments that cholesterol prepares the Hh protein to deliver its message by reacting with the molecule, cleaving it, and then remaining bound to the now-active half (*Science*, 11 October 1996, p. 255). This was the first time anyone had seen cholesterol form a strong, covalent bond with a protein. It also got Beachy wondering whether cholesterol abnormalities could sabotage development in the same way as defects in Shh itself do.

The researchers looked in the literature for clues that might help them connect what they had learned about cholesterol and Shh signaling with HPE. They struck pay dirt when they found reports of two classes of teratogens—compounds that induce birth defects—that mimic the effects of eliminating the *Shh* gene. Compounds in one group, which Charles Roux and colleagues showed over 30 years ago can induce HPE in rats, are known to interfere with the body's production of cholesterol. The other compounds came to light in the 1950s and early 1960s, when Richard Keeler and Wayne Binns traced a high incidence of cyclopia in lambs to chemicals in the plant *Veratrum californicum*, or corn lily, which the ewes had eaten. These compounds resemble cholesterol structurally.

Beachy's team members reasoned that all of these teratogens somehow interfere with cholesterol's ability to perform the function they had observed in the test tube: activating and binding Shh. But they were about to get a surprise. Both Beachy's group and the team of John Incardona, Raj Kapur, and Henk Roelink at the University of Washington, Seattle, found that what these compounds actually do is render cells that receive the Shh signal unable to respond properly. The finding shows, says Beachy, that "there are at least two different roles for cholesterol in the [Shh] pathway. It's important for both the signaling protein and in the target cell."

This new role for cholesterol in Shh signaling emerged in Beachy's lab after Jeffery Porter, currently at Ontogeny Inc. in Cambridge, Massachusetts, and Michael Cooper treated cells and embryos with the teratogens and traced what happened to the Shh protein. The team found that the toxins did not affect the size of the molecule—suggesting it was being cleaved and modified properly—or where it ended up in the embryo. But "what really knocked our socks off," says Beachy, is what happened when Cooper added the compounds along with purified active Shh to a piece of neural tissue from a chick embryo that cannot make the protein but can respond to it. The cells ignored the Shh protein, failing to turn on and off the genes that Shh normally controls. "There's an active signal present but no response," says Beachy. "The defect induced by the compounds must be in the responding tissue."



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A role for cholesterol? Cyclopian lamb.

A clue to the defect came when the researchers took a closer look at cells treated with the compounds and found an unusual distribution of sterols—cholesterol and related molecules. A "river of sterols," as Beachy describes it, normally travels back and forth between the cell surface and the endoplasmic reticulum (ER)—the cellular compartment where cholesterol is made. The teratogens apparently dam up this river: Cholesterol builds to excessive levels on the cell surface, while levels in the ER appear unusually low.

It makes sense that defective sterol trafficking might interfere with Shh signaling, says Beachy. A target cell protein called Patched, which binds Shh and plays a critical role in signaling, contains a stretch of amino acids that resembles the sterol-sensing domains in several other proteins. These proteins, which help regulate the cholesterol levels in the cell, use the domains to measure the amount of sterols present and adjust cholesterol production accordingly.

No one yet knows for certain how to explain the new observations, says Beachy, but he proposes that a shortage of cholesterol at the ER, detected by the sterol-sensing domain of Patched, might lock the protein into an inactive state and keep it from relaying the Shh signal. "Cell proliferation is often a part of the response to Hedgehog proteins," says Beachy. "Maybe a cell monitors cholesterol levels before it responds to Hedgehog," to ensure that it has enough cholesterol to make new cell membranes. "That kind of system could allow the cell to ask, 'Am I making enough?' " before it goes on to multiply. If not—or if a teratogen has interfered with cholesterol trafficking within the cell—Patched shuts down the pathway, and development goes awry.

It's a plausible scenario, says William Mobley, a neuroscientist at Stanford University School of Medicine: "We have to start thinking of sterols as molecules that impact the function of signaling proteins within cells." Incardona, however, thinks the teratogens' effect on cholesterol isn't the full story. He thinks that at least some of the compounds may interfere directly with Patched or some other component of the cell's response to Shh. "The trafficking defect may not be the main teratogenic effect," he says. "In my hands, the plant compounds are teratogenic at concentrations well below those where they cause trafficking defects."

New studies of genetic HPE are reinforcing the connection between cholesterol and development. For example, mice that lack the gene for megalin, a cell surface protein that binds and internalizes cholesterol, show signs of HPE. Genetic aberrations that result in faulty cholesterol metabolism also may contribute to human HPE, as a disorder known as Smith-Lemli-Opitz syndrome (SLOS) indicates. SLOS patients have developmental delays, mental retardation, and, in some 5% of patients, HPE. They accumulate a biochemical precursor of cholesterol, and several recent studies on these patients have identified mutations in the gene for the enzyme that converts this precursor into cholesterol.

So can eating a cholesterol-rich diet reduce the risk of birth defects in mothers at risk for having babies with HPE? In mother rats exposed to the teratogenic compounds that inhibit cholesterol biosynthesis, it apparently can, says Richard Kelley, a human geneticist at Johns Hopkins. "This really makes you wonder whether the mother's cholesterol metabolism will influence the severity of HPE in humans." Kelley is quick to add that there are big differences in how rat and human mothers transport nutrients to embryos, and that consuming a lot of cholesterol doesn't mean it will reach the embryo. But such musings are sure to be put to the test as researchers explore cholesterol's surprising new role.

–Evelyn Strauss

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