the hillside, perching on a 10-story-high scaffolding for their analysis. They focused on layers 10 and 4, previously noted for putative king-sized hearths. They cleaned the exposure, studied the sediments microscopically, and used infrared spectrometry onsite to analyze the chemical constituents of sediments and fossil bone. In the lab, they confirmed that a small number of bones were burned. But the sediments contained no ash or siliceous aggregates, soil-derived minerals that are cemented together in trees and stay intact after burning—and should be present at the site of almost any wood fire. The thick layers aren't ash at all, but accumulations of organic material, much of it laid down under water, says Weiner.

The team did find stone tools closely associated with burnt mammal bones. And more of these bones came from large animals than small, a proportion considered consistent with human activity, because people are more likely to roast horse than mice for dinner. But although this clearly indicates the presence of fire somewhere nearby, it doesn't convince most researchers that humans rather than nature sparked the flames. That's part of the reason why even older purported evidence of fire—up to 1.8 million years old—from sites in Africa and Asia has been considered "dubious," says paleoanthropologist Philip Rightmire at the State University of New York, Binghamton. "The whole thing is [now] ambiguous, and that's the normal situation," adds anthropologist Lewis Binford of Southern Methodist University in Dallas, who visited Zhoukoudian briefly in the 1980s and first challenged the interpretation of hearths.

The paper also raises questions about whether humans actually lived at the site, because the researchers describe it not as a traditional cave but as the enlargement of a vertical fault, open to the sky. "This is an important reinterpretation," says Potts. "It means that, who knows, maybe it wasn't a home." Anthropologist Alison Brooks at George Washington University in Washington, D.C., who has also worked at the site, goes further: "It wouldn't have been a shelter, it would have been a trap." Taken together, the evidence "brings Zhoukoudian a good deal more in line with sites from around the world, with a low fingerprint of human activity," says anthropologist Chris Stringer of the Natural History Museum in London.

The first strong evidence of purposeful use of fire is now associated with much younger humans. "This puts it forward at least to *H. heidelbergensis* and may push it forward to Neandertal," says Brooks. A leading candidate may be Vértesszöllös, Hungary, an *H. heidelbergensis* site between 400,000 and 200,000 years old, where burned bone is arranged in a radial pattern as if around a campfire. "That spatial evidence is missing for Zhoukoudian," says Potts.

Still, some scientists advise against drawing sweeping conclusions from this single study. "The researchers were limited by the area they sampled," far from the center of the cave, points out Huang. "Therefore, it is not an ideal place to detect the evidence of controlled fire use," adds Gao Xing, an archaeologist formerly with the IVPP and now at the University of Arizona, Tucson.

Nonetheless, ambiguity at Zhoukoudian raises questions about whether *H. erectus* anywhere used fire, Stringer says. Yet the species somehow survived in Zhoukoudian's temperate climate and colonized lands even farther north. The absence of fire suggests that *H. erectus* was much less advanced, argues Brooks. But other recent discoveries have suggested that the species was a sophisticated toolmaker, points out Huang, and perhaps even traveled by boat (*Science*, 13 March, p. 1635). For now, the dampened flame at Zhoukoudian has thrown these ancient humans into deeper shadow. "This work is another new beginning, but it is not enough to answer all the questions we are curious to know," says Huang.

–BERNICE WUETHRICH

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MEETING SOCIETY FOR DEVELOPMENTAL BIOLOGY

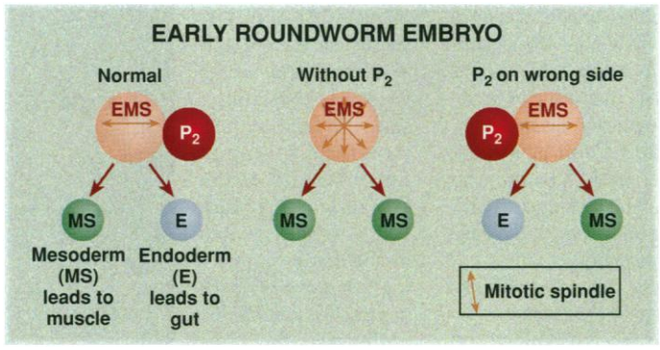
How Embryos Shape Up

About 800 biologists gathered at Stanford University from 20 to 25 June for the 57th annual meeting of the Society for Developmental Biology. Study organisms ranged from flies to mice to plants, but there was plenty of common ground, including a new pathway by which signaling molecules can shape the early embryo and a new gene that helps specify right from left.

WNT Takes a New Path

In development, as in so much of biology these days, the gene's the thing: Researchers probe which genes turn on and off as embryos develop and which signaling molecules push the genetic switches. But surprising results presented at the meeting show that at least one classic signal, the wingless (WNT) protein, can guide development without touching those switches. At a crucial moment in development, WNT triggers an early cell to divide asymmetrically into two daughter cells, which later give rise to different sets of tissues. The new results, reported in a plenary session by developmental geneticist Bruce Bowerman of the University of Oregon, Eugene, and his colleagues, suggest that WNT does so by bypassing the genes and acting directly on the cell's internal skeleton.

The result establishes a new modus operandi in developmental biology signaling pathways. WNT, which is perhaps best known for helping to create pattern in insect appendages, manages this feat at least in part by sending a signal down a chain of molecules to the nucleus of its target cell, where it activates specific genes. Now, says Norbert Perrimon, a developmental geneticist at Harvard Medical School in Boston, "Bruce has provided some really convincing data that proteins in the WNT pathway directly control the cytoskeleton without [turning on genes]." The finding also makes developmental researchers reconsider the cytoskeleton. "The cytoskeleton [as] a direct signaling target has not been on people's radar screens," says William Talbot, a developmental geneticist at New York University's Skirball Institute of Biomolecular Medicine. "Normally you get a signal, figure out how it gets to the nucleus, and then you think you're done. Certainly we have to think about the cytoskeleton now."



SOURCE: B. BOWERMAN

Division with a difference. Only after getting a message from a nearby P_2 cell can the EMS cell divide so that one daughter can become endoderm.

Bowerman made his discovery in the roundworm *Caenorhabditis elegans*, where researchers had already shown that at the four-cell stage of development, one cell, called P_2, delivers an important message via the WNT pathway to its neighbor cell, called EMS because it gives rise to both en-

doderm and mesoderm. According to the current model, P_2 orders EMS to distribute its contents so that when the cell divides, it yields two distinct offspring. The daughter cell closest to P_2 (named E, for endoderm) makes tissue that becomes gut, and the other daughter (named MS, for mesoderm) makes tissue that becomes muscle. Without P_2 next door, EMS gives rise to two MS cells.

Just how the WNT signal skews EMS division wasn't clear. But P_2 was known to control the orientation of EMS's mitotic spindle—the array of skeletal fibers that pulls apart the chromosomes as the cell divides. This might be how P_2 forces EMS to generate its distinct daughters, reasoned developmental biologist Bob Goldstein, currently at the University of California, Berkeley, who did the original P_2 signaling work. If the mitotic spindle is oriented correctly, then one daughter might get a different batch of cytoplasmic material from the other.

To find out whether the WNT pathway dictates the axis of spindle formation, Ann Schlesinger, a graduate student in Bowerman's lab, did experiments using a variety of EMS and P_2 cells, some normal and some having mutations in the WNT pathway. When she put mutant P_2 next to normal EMS or vice versa, the spindle formed at random angles relative to P_2, showing that spindle orientation does require the WNT pathway.

Next, Schlesinger blocked all transcription—the activation of genes by transcribing their DNA into messenger RNA—in both EMS and P_2, using a chemical called actinomycin D. She saw "perfectly normal spindle orientation" relative to P_2, showing that the WNT signal was getting through even though the cell couldn't turn on any new genes. "You don't have to go through the nucleus and activate genes," says Bowerman. Instead, WNT seems to act on the spindle directly, targeting molecules that must already be in the cell.

The next step will be to identify those molecules, says Stuart Kim, a developmental biologist at Stanford University. "It's very exciting," he says. "Bruce has several genes that seem to play similar roles [in affecting EMS division] as the WNT genes, but they don't appear to be known WNT pathway genes. Maybe these will be involved in directing the cytoskeletal events."

Even though the WNT signal seems to bypass the nucleus in directing EMS division, it may ultimately circle back to the genes in later cell generations. The daughter cells presumably have different fates because they apportion the cytoplasm in such a way that one of the cells has what it takes to develop into endoderm. The still-mysterious components of this cytoplasm might then direct different patterns of gene expression in the daughters. Says Bowerman: "Instead of going to the cytoskeleton through the nucleus, we're suggesting that, at least in some cases, you go to the nucleus through the cytoskeleton."

Putting a Heart in the Right Place

Hearts must learn left from right early in their development. Like many other organs, a normal heart is asymmetric, located on the left side of the body, with veins and arteries hooked up so blood flows in one way and out the other.

Researchers had already identified some of the steps in a genetic signaling pathway that helps define right and left in an embryo long before anyone looking at it can see a difference. And at the meeting, two independent presentations—a talk and a poster—announced the first candidate for a molecule that may actually translate this signal into an asymmetric heart. *Pitx-2* (also known as *Ptx2*), the gene that produces the molecule, is activated only on the left side of frog, mouse, and chick embryos, persists there as the organs develop, and controls the position of the heart and gut.

"This gene is very important, because it's not just a marker but actually has a function," says Leonard Zon, a geneticist and hematologist at Children's Hospital in Boston. "Left-right asymmetry is fundamentally related to heart formation, and people are racing to try to understand how it works," in part because it may help explain congenital birth defects in which organs are reversed.

Biologists already knew that a gene called *nodal* appears to direct the developing heart and other organs to their proper left-right locations. But *nodal* is turned on—in some cases by the patterning molecule Sonic hedgehog (Shh)—and then off before any visible asymmetry appears, so scientists reasoned that it must signal another gene or genes.

The two groups represented at the meeting weren't looking for genes that direct heart asymmetry when they found *Pitx-2*, but it attracted their attention because it's expressed only on the left side of the embryo. Cliff Tabin's lab at Harvard Medical School in Boston, working on chicks, and Martin Blum's lab, at Forschungszentrum Karlsruhe Institute of Genetics in Germany, working on frogs and mice, independently presented work showing that *Pitx-2*'s leftward bias is what skews the heart and gut.

A heart starts out as a straight tube; the first visibly asymmetric step in its development occurs when that tube curls or "loops" to the right into an S-shaped structure (see diagram); the direction of looping helps specify where the heart will end up in the body. Both Tabin and Blum found that early in development, *Pitx-2* appears on the left side of the tube. Tabin also found that in chicks, the portion of the heart derived from the left side of the tube expressed *Pitx-2*. The findings imply that in chicks, frogs, and mice, *Pitx-2* stays on long enough and in the right places to shape the heart.

The researchers next showed that *Pitx-2* responds to the signals that control left-right patterning, the *Shh/nodal* pathway. They introduced nodal or its frog relative into the right side of young chick or frog embryos and found that *Pitx-2* was expressed not only on the left but also on the right. Tabin's group next introduced antibodies that inactivate *Shh* into the left side of the embryo and found no *Pitx-2*. These results showed that the *nodal* signaling pathway can turn *Pitx-2* both on and off.

But can the gene actually control organ formation? To find out, Tabin blocked normal *Pitx-2* expression with antibodies against Shh, while artificially producing Pitx-2 on the right side of the embryo with a virus that carries the gene. Some of the resulting embryos grew heart tubes that looped in the wrong direction. "*Ptx2* by itself is sufficient, in [the] absence of other signaling, to drive the looping to the left," Tabin said. Blum confirmed Tabin's results in frogs: He injected mouse Pitx-2 into cells on the right side of a frog embryo and later saw heart and gut tubes that looped incorrectly.

Although it's possible that *Pitx-2* turns on yet another gene, "these results give you the feeling that there might be a direct connection between *Ptx2* and organ development," says Kathryn Anderson, a developmental geneticist at the Sloan Kettering Institute in New York. "You don't need to invoke five more steps between *Ptx2* and the ability to set up asymmetry." *Pitx-2*, it seems, lies at the heart of hearts.

–EVELYN STRAUSS

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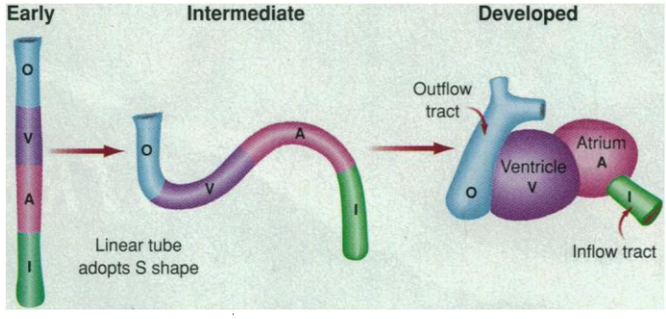

Heart shaped. Normal development of a frog heart involves an asymmetric shape, driven apart by lopsided expression of the *Pitx-2* gene.

ILLUSTRATION: P. MORRIGHAN SOURCE: BLUM *ET AL.*