

DEVELOPMENTAL BIOLOGY

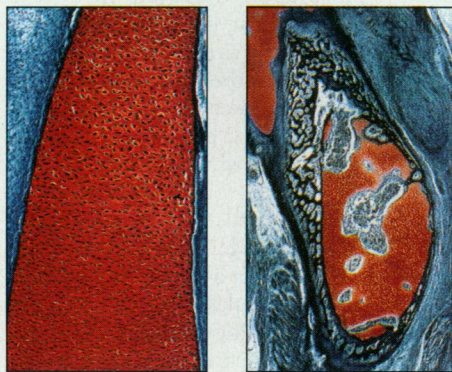
Putting the Brakes on Bone Growth

Human life starts with an astonishing growth spurt: The long bones of the average infant lengthen by 50% during the first year after birth. That growth rate drops to about 7% per year by age 3—which is just as well, or children would surge past the 6-foot (183-cm) mark while in nursery school. But just how nature moderates this bone growth—thus keeping the world free of 4-year-old Wilt Chamberlains—has been a long-standing mystery. Now, by combining their results, three teams of researchers in Boston may have found the beginnings of an answer.

Researchers have long known that long bones form when some chondrocytes—proliferating cartilage cells in the growth plates at the end of long bones such as a femur or humerus—stop dividing, enlarge, and differentiate into a scaffold for new bone cells. Work on mouse and chick embryos, reported on pages 613 and 663 of this issue, has revealed a cycle of gene-protein interactions that puts the brake on this differentiation process, allowing only a few chondrocytes at a time to stop dividing. When the researchers release this brake by removing components of the cycle, the entire growing area differentiates, before the cartilage cells that would have given bones their full length have arisen, thus creating animals with stubby limbs.

The scientists speculate that controlled changes in this cycle may cause the more gradual deceleration of bone growth in children. The findings also suggest, says Arthur Broadus, an endocrinologist at Yale University, that “if chondrocyte differentiation proceeds too quickly or too slowly, you get abnormalities of the long bones,” such as those in some kinds of dwarfism.

The long bone story began to fuse last year in the laboratory of molecular biologist Cliff Tabin at Harvard Medical School, where developmental geneticist Andrea Vortkamp was studying Indian hedgehog (Ihh), a signaling molecule whose precise function was unknown. Working with chick embryos, Vortkamp found that Ihh is produced by cells making the transition to enlarged or “hypertrophic” chondrocytes. She also found that adding extra Ihh slows the rate at which chondrocytes differentiate, and that the intended recipient of the Ihh signal is the perichondrium, a sheath of tissue enclosing long bones. Together, these findings suggested that Ihh is part of a negative feedback loop that assures slow, steady bone growth. Tabin and Vortkamp reasoned that Ihh from differentiating chondrocytes must activate some unknown signaling protein in the perichondrium, which in turn acts on the growth plate to prevent more chondrocytes from differentiating.



Boning up. In a normal chick embryo (left), cartilage cells (red) turn slowly into bone (blue); in the mutant embryo (right), cells differentiate all at once.

Meanwhile, two teams of endocrinologists, including Henry Kronenberg, Beate Lanske, and Gino Segre, all at Massachusetts General Hospital, were investigating another recently discovered signaling molecule, parathyroid hormone-related protein (PTHrP). They had found that this protein is produced mainly in the perichondrium at the end of long bones, that receptors for it are present in proliferating chondrocytes, and—most importantly—that chondrocyte differentiation is accelerated in mice genetically engineered to lack either

PTHrP or its receptor.

These two lines of research converged in September 1995, when Tabin described his and Vortkamp's theory at a meeting. Kronenberg was in the audience and “nearly fell out of his chair, because his lab was already pursuing a protein with all the effects we had predicted,” says Tabin.

A few more experiments completed the picture, showing that PTHrP is indeed the missing signal in Tabin's scenario. Vortkamp found that adding extra Ihh to chick wing bones increases the production of PTHrP in the perichondrium. And Kaechoong Lee of Segre's lab showed that the premature differentiation of chondrocytes in tissue from mice engineered to lack the gene encoding PTHrP can be reversed by adding purified PTHrP. But adding hedgehog protein has no effect, indicating that Ihh's influence must be mediated by PTHrP.

But the story of bone-growth regulation is not yet complete. It is unclear how the growth-restraining Ihh-PTHrP feedback loop interacts with growth-enhancing signals thought to be provided by other proteins, notes Tabin. And new mouse and chick experiments are needed to explore whether the slowing of long-bone growth in children and its eventual cessation at the end of adolescence result from a change in the strength of the Ihh-PTHrP loop. Says Kronenberg: “We're just beginning to understand the fine-tuning of this system.”

—Wade Roush

PHYSICS

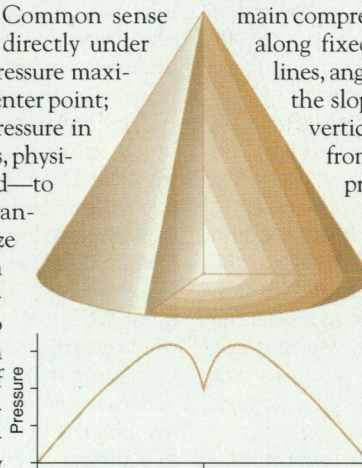
Searching for the Sand-Pile Pressure Dip

The humble sand pile is to granular mechanics what Fermat's Last Theorem was to number theory: a tantalizingly simple problem that stubbornly eludes a solution. The question is this: Where does a conical pile of poured sand exert its maximum amount of pressure on the ground? Common sense would say in the middle, directly under the apex, but in fact the pressure maximum is a ring around the center point; there is actually a dip in pressure in the middle. And for 15 years, physicists have tried—and failed—to produce a complete explanation. “It's alarming to realize that for what looks like a completely classical problem there seems to be no obvious approach within the existing framework of classical continuum mechanics,” says physicist Michael Cates of the University of Edinburgh in the U.K.

Now Cates thinks he has a new way to attack the prob-

lem, but it is causing a bit of a flap in the field. Last week in *Nature*, along with Edinburgh colleague Joachim Wittmer and Philippe Claudin and Jean-Philippe Bouchaud, both of France's Atomic Energy Commission at Gif-sur-Yvette, Cates proposed that the main compressive stresses in a sand pile lie along fixed parallel lines. These stress lines, angled precisely halfway between the slope of the pile surface and the vertical, steer the pile's weight away from the center, giving a central pressure dip.

Despite its simplicity, the model does a respectable job of reproducing experimental data. “[It's] a miracle that there is such an agreement with experiment,” says Hans Herrmann of the Institute of Computer Applications at the University of Stuttgart in Germany, who has worked on computer simulations of sand piles. But given the problem's



Piling on the pressure. Do stress lines in a sand pile steer pressure away from the center?