He went on to outline several conceivable resolutions to the problem. One possibility is that the terms for the energies somehow come within a hair's breadth of canceling but don't quite do so, leaving just enough residual energy to explain the constant. But Weinberg, and some other physicists, have a hard time swallowing the idea that the entire universe could be founded on such an unlikely balancing act. Weinberg's response: the so-called anthropic principle, which holds—in logic that many physicists find circular—that fundamental constants have the values they do because only those values allow human beings to exist and measure them.

The principle, which many cosmologists trace back to work by Princeton University's Robert Dicke in the 1960s, assumes multiple universes à la Gott—or multiple regions within a single universe—in which parameters like the cosmological constant have different values, making the laws of physics different in different spots. In most of these universes the cosmological constant would take on higher, more plausible values. Our own universe would be peculiar not because of a single mind-bending coincidence but because humans can exist only in those rare universes or regions with tiny cosmological constants. Weinberg's conclusion: "The only kind of theory that is today respectable in which you can understand the cosmological constant problem is theories based on some kind of anthropic reasoning."

Although no one ventured to debate Weinberg formally, Turner declared himself "amazed" by the approach. "It's really throwing your hands up on the problem." But Weinberg suggested a way to test the anthropic approach. Higher values of the cosmological constant would be more common in the plethora of universes, so if the cosmological constant in our own universe turns out to be close to the largest values compatible with galaxy formation, "it will be, for me, incomprehensible on any other grounds but the anthropic principle," he said.

With issues like the cosmological constant and the anthropic principle catching fire even as old conflicts die out, there will be no shortage of topics for future versions of the Princeton conference. In his introductory talk, Martin Rees of the University of Cambridge asked his audience to keep in mind that "as the consensus advances, new questions which couldn't even have been posed in earlier decades are now being debated." At that rate the rabbi's wise words will echo in cosmology for some time to come.

–James Glanz

GENETIC DISEASE

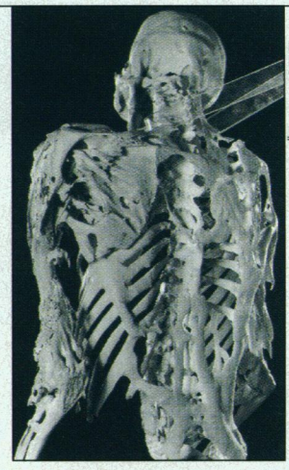
Protein Builds Second Skeleton

In Greek myth, one glance at Medusa's snake-coifed head could turn a man to stone. But the villain in a rare inherited disease that relentlessly converts the body's soft connective tissues into bone—transforming its sufferers into living statues—has proved to be much more elusive. Indeed, it lurks within the victims' own immune systems, scientists in Philadelphia have discovered.

In children with the disease, called fibrodysplasia ossificans progressiva (FOP), the slightest injury to ligaments, tendons, or muscles can cause severe inflammation, followed by the appearance of cartilage, and then ordinary bone, at the site of the injury. As the disease progresses, sufferers' spines, limbs, rib cages, and jawbones fuse in place, leading to complete immobilization.

In the 22 August *New England Journal of Medicine*, a team led by orthopedic surgeon Frederick Kaplan of the University of Pennsylvania School of Medicine now reports that this abnormal bone buildup occurs because the lymphocytes, or white blood cells, of people with FOP erroneously manufacture bone morphogenic protein–4 (BMP-4), a powerful signaling protein known to help build the skeleton of the developing embryo. "You should be able to repair and remodel bone later in life, but you shouldn't be able to make a new bone," Kaplan says. "That's what's happening here."

While developmental biologists have been studying BMPs and related proteins in organisms from fruit flies to humans since the 1960s, this is the first time a member of the BMP family has been implicated in a human genetic disease. "It's an amazing story," says developmental geneticist William Gelbart of Harvard University, who discovered the first BMP family member, the protein Decapentaplegic (DPP), which helps establish body and limb axes in the developing fruit fly, among other functions. "It's incredibly gratifying to see how central these molecules are in a whole host of developmental processes—and now in a human disease with heartbreaking effects." The discovery could eventually lead to a therapy to block either the production of BMP-4 or its effects.



JOANN DEITHORN/MÜTTER MUSEUM

Bony prison. FOP fused the spine, shoulders, ribs, and elbows of this man, who died of pneumonia at age 39.

The idea that a gene defect might underlie FOP originated about 7 years ago, Kaplan says, after he and geneticist Michael Zasloff, also at the University of Pennsylvania, found a small family in which both a parent and children were affected, indicating that the disorder is hereditary. In 1990, after learning that DPP's relatives, the newly discovered human proteins BMP-2 and BMP-4, help build limbs in the mammalian embryo by triggering bone-cell formation, Kaplan and Zasloff proposed that FOP might be caused by a genetic mutation affecting the production of one of the BMPs.

A test of the hypothesis had to wait until 1993, when Kaplan and Zasloff first obtained blood and tissue samples from patients with FOP. Penn medical student Adam Shafritz, now a resident physician at Manhattan's Hospital for Special Surgery, examined the samples, looking for messenger RNAs that would indicate that the BMP genes were active. He found one—corresponding to the BMP-4 gene—in the lymphocytes of 26 of 32 FOP patients studied, but in only one of 12 normal subjects.

That finding posed a puzzle, however, because if the lymphocytes were releasing BMP-4 into the bloodstream, it would be so diluted and short-lived that it couldn't account for new bone growth in discrete locations around the body. Then, Kaplan recalls, the team found "the Rosetta stone for this whole condition": a biopsy sample taken 25 years earlier from a 4-year-old boy with FOP.

Under the microscope, the researchers saw masses of lymphocytes surrounding and choking off muscle cells. While a normal response to injury, in FOP patients, the researchers realized, this clumping must create high local concentrations of BMP-4, triggering bone growth. The lymphocytes of people with FOP, Kaplan and Zasloff conclude, probably carry a genetic error that improperly switches on production of BMP-4.

The researchers have now set out to locate this error, which may be in the regulatory regions of the BMP-4 gene itself or in some other gene whose product controls BMP-4 production. Already, however, the findings have heightened hopes for an eventual cure for FOP. "With so much being discovered about how the BMPs act," says Brigid Hogan, a developmental geneticist at Vanderbilt University in Nashville, Tennessee, "it might be possible to develop drugs that would block some part of the BMP-4 pathway—and therefore prevent the progression of what is a horrible, nightmare disease."

–Wade Roush