Human Skeletal Growth Factor Isolated

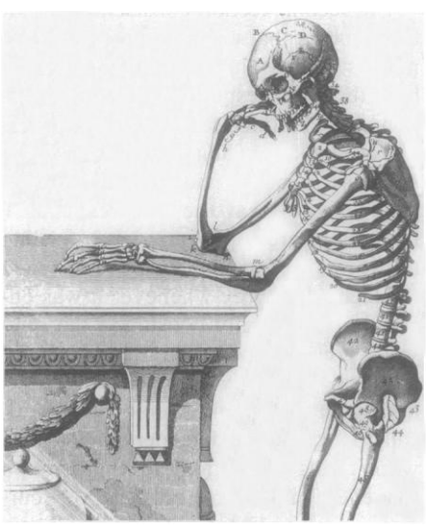
A large molecule that regulates the growth of bones has now been isolated from humans as well as animals

A protein that stimulates the growth of human bone cells and embryonic chick bones has been isolated from human bones by John R. Farley and David J. Baylink of Loma Linda University and the Jerry L. Pettis Veterans' Hospital in Loma Linda, California. Isolation of the protein, called human skeletal growth factor (hSGF), was carried out at the American Lake Veterans Administration Hospital in Tacoma, Washington, and is reported in the most recent issue of *Biochemistry*.* Baylink and Farley and other investigators have previously isolated related materials from animal bones and cells, but this is the first unequivocal demonstration that such a substance exists in humans.

In humans and animals, bone is in a constant state of flux: old or damaged bone is resorbed (dissolved) and new bone synthesized to replace it. In the healthy adult, these processes are in balance. In certain disease states, such as osteoporosis and periodontal disease (*Science*, 8 February 1980, p. 628), resorption predominates and the bones become less dense than normal and, consequently, more fragile. Baylink speculates—although some scientists think the evidence is still circumstantial—that the process of bone resorption and replacement is mediated, at least in part, by a chemical that is released during bone resorption; this coupling agent could then stimulate the synthesis of new bone. Several bone diseases might result from insufficient synthesis, inadequate storage, or defective receptors for this coupling agent. Although Baylink and Farley are not yet prepared to say that hSGF is the coupling agent, it appears to fill all the necessary criteria.

The growth factor was isolated from human femoral heads obtained at hip replacement surgery. The bone was first crushed and demineralized. The residue was then homogenized in a phosphate buffer, and hSGF was isolated by selective heat and acid precipitations, chromatography, and electrophoresis to produce a homogeneous protein with a size of 83,000 daltons. When this material was treated with a detergent, Baylink and Farley observed one major subunit with a mass of 65,000 daltons and two smaller ones. These have not yet been tested for biological activity.

The protein is a potent growth factor for bone cells at low concentrations. A level of 0.3 microgram per milliliter increases DNA synthesis in a standard cell proliferation assay to 231 percent of controls. The same concentration increases the growth rate of cultured embryonic chick tibiae and femurs to 164 to 185 percent of controls and cultured human bone cells to 1090 percent of controls. The agent has little effect, however, on other types of cells. The molar concentration at which hSGF is effective is comparable to the effective concentrations of other mitogens, such as epidermal growth factor, fibroblast growth factor, insulin, and somatomedin.



The large size of hSGF is rather unusual; most other mitogens are smaller, less than 15,000 daltons. Baylink and Farley have, however, previously isolated a similar protein, which they call putative chick skeletal coupling factor or cSCF, that is about 75,000 daltons, as well as similar material from cows and rats. The activity of these proteins is very similar to that of hSGF.

Ernesto Canalis and Lawrence G. Raisz of the University of Connecticut Health Center and William A. Peck of the Washington University School of Medicine have previously isolated two related proteins from cultured embryonic rat bone cells. One, with a mass of about 25,000 daltons, stimulates DNA synthesis and is very similar to platelet derived growth factor. The second, with a mass of about 10,000 daltons, stimulates synthesis of collagen, and is similar to somatomedin. The two agents have not been tested on cells other than cartilage and chondrocytes, so their specificity is not known. These agents may be specialized fetal proteins related to adult skeletal growth factors.

Marshall R. Urist of the University of California, Los Angeles, in contrast, has isolated a 17,000-dalton protein from rabbit, cow, and human bone. This material, called bone morphogenetic protein (BMP), has some of the stimulatory effects associated with hSGF, but its primary function is to induce bone cell differentiation. Implanted in muscle tissue, for example, BMP induces perivascular connective tissue (mesenchymal type cells) and other unspecialized cells to become bone cells. The two growth factors may thus be complementary, Urist says: BMP initiates the differentiation of new bone cells and hSGF regulates the total number produced. As a mitogen, BMP is less active than hSGF in Baylink and Farley's assay.

The new results tie in well with some other observations. Julie Glowicki and Judah Folkman of the Children's Hospital Medical Center in Boston and Urist have found that demineralized bone can be used in animals and humans to repair bone defects. It seems likely that the bone acts as a template for the formation of new bone and that some substance released by the bone matrix, possibly hSGF, BMP, or both, stimulates the growth of new bone cells.

Baylink and Farley are now working to produce antibodies to hSGF—not an easy task since bone proteins are generally weak antigens. They have had some success by modifying the protein and have begun testing for hSGF in blood. They have already found that the concentration of hSGF is elevated in patients with Paget's disease, a chronic disorder characterized by enlargement and deformity of the skull, spine, and long bones. They are also labeling the protein so that they can trace its course through the body and look for receptors. In preliminary experiments with Guy Howard of the Tacoma veterans hospital, they have found strong binding sites only in bone cells.

—THOMAS H. MAUGH II

*J. R. Farley and D. J. Baylink, *Biochemistry* **21**, 3502 (1982); J. R. Farley, T. Masuda, J. E. Wergedal, D. J. Baylink, *ibid.*, p. 3508.

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