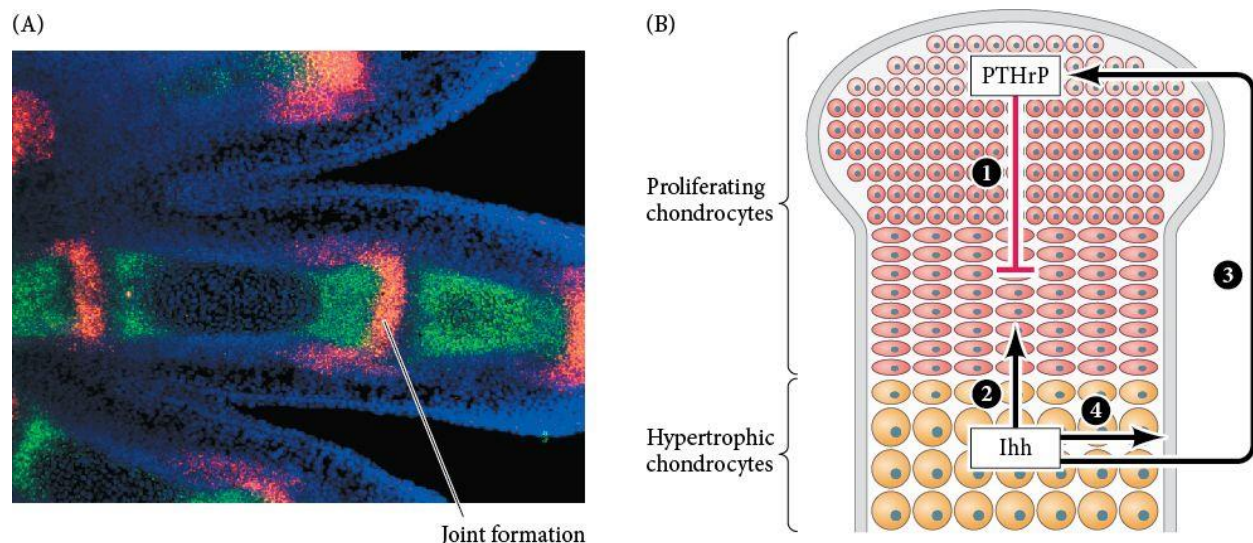


Continued Limb Growth: Epiphyseal Plates

The three axes of human limbs are specified in a highly asymmetrical fashion. However, their growth over the next 16 years is so symmetrical that the length of one arm matches the other to within 0.2% (Ballock and O'Keefe 2003; Wolpert 2010). If all our cartilage were turned into bone before birth, we could not grow any larger, and our bones would be only as large as the original cartilaginous model. But growth zones—epiphyseal plates—form at the proximal and distal ends of each developing long bone. At the portion of the epiphyseal plate farthest from the new bone is a germinal region of cartilaginous stem cells, followed by regions of proliferating cartilage cells, mature cartilage cells (chondrocytes), and hypertrophic cartilage cells. The hypertrophic cartilage cells (which increase their size five- to tenfold) undergo apoptosis and are replaced by bone cells (osteocytes).

In the long bones of many mammals (including humans), endochondral ossification spreads outward in both directions from the center of the bone (Figure 1). Although more than 10,000 new cartilage cells may be made daily, the number appears to be identical in each arm. Cartilage proliferation in humans is high through about 3 years of age. The major factor of differential growth (between the arms and legs of a human or between the legs of a human versus the legs of a dog), however, is probably the swelling of the hypertrophic cartilage. Not only can different numbers of cartilage cells be made, but those cells can enlarge to different sizes (Cooper et al. 2013). After a growth spurt at puberty, the epiphyseal growth plates fuse, and there are no longer any stem cells for growth. As long as the epiphyseal plates are able to produce chondrocytes, the bone continues to grow.



A courtesy of Dr. P. Tylzanowski. B after H. M. Kronenberg. 2003. *Nature* 423: 332–336.

Figure 1 Model for endochondral ossification in the limb. (A) In situ hybridization in the limb of a 21.5-day mouse embryo shows *collagen-2* mRNA (green) in the proliferative growth plate cartilage and *GDF5* mRNA (red) in the region destined to become a joint. Nuclei are stained blue. (B) Regulation of cartilage cell proliferation by PTHrP (parathyroid hormone-related protein) and Indian hedgehog (Ihh). (1) PTHrP acts on receptors on proliferating chondrocytes to keep them dividing and

thereby delays the production of Ihh. (2) When the source of PTHrP production becomes sufficiently far away, Ihh is synthesized; Ihh acts on its receptor (present on chondrocytes) to increase the rate of chondrocyte proliferation and (3) to stimulate the production of PTHrP at the ends of bones. (4) Ihh also acts on the perichondrial cells enveloping the cartilage, converting them into the osteoblasts of the bone collar. (A courtesy of Dr. P. Tylzanowski; B after Kronenberg 2003.)

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