

articular cartilage were positive for IGF-1 and IGF-1 receptor in all animals with osteoarthritis in each grade. In the moderate group, in which articular cartilage degeneration had progressed further, the presence of IGF-1 and IGF-1 receptor was noted not only in fibroblastic-like cells, but also in chondrocytes clustering in a layer deeper than fibroblastic-like cells. In contrast to chondrocytes in the weight-bearing regions, these chondrocytes proved to have a very high mitotic activity in this study. Therefore, it can be speculated that chondrocytes presumed to be differentiated from totipotent immature mesenchymal cells may have produced a cartilage matrix by the autocrine mechanism via IGF-1. A previous report has demonstrated that more IGF-1 is present in human osteoarthritis cartilage and synovial fluid than in normal cartilage and synovial fluid, and suggested that this IGF-1 originated from the synovial membrane (Schneiderman et al., 1995). However, this study could not demonstrate that IGF-1 secreted by totipotent immature mesenchymal cells directly participated in the differentiation to chondrocytes. Some studies have indicated the close involvement of TGF-beta 1 in experimental osteophyte formation (van Beuningen et al., 1994; van den Berg, 1995), and speculated that TGF-beta 1 has a facilitatory effect on differentiation of totipotent immature mesenchymal cells. Furthermore, other growth factors are also thought to interact in a complicated manner (Trippel, 1995).

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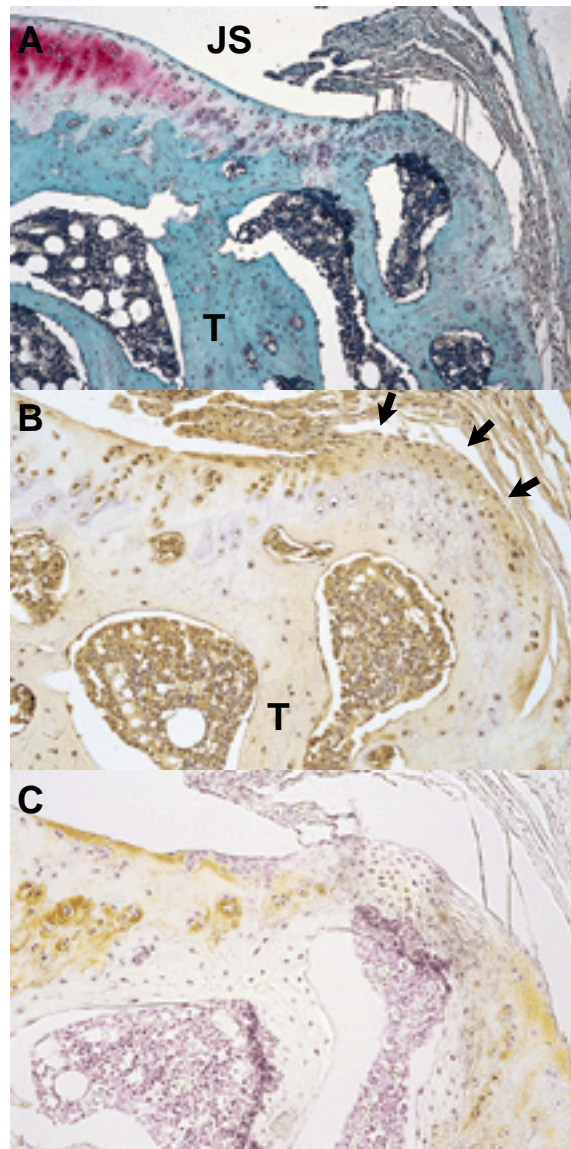
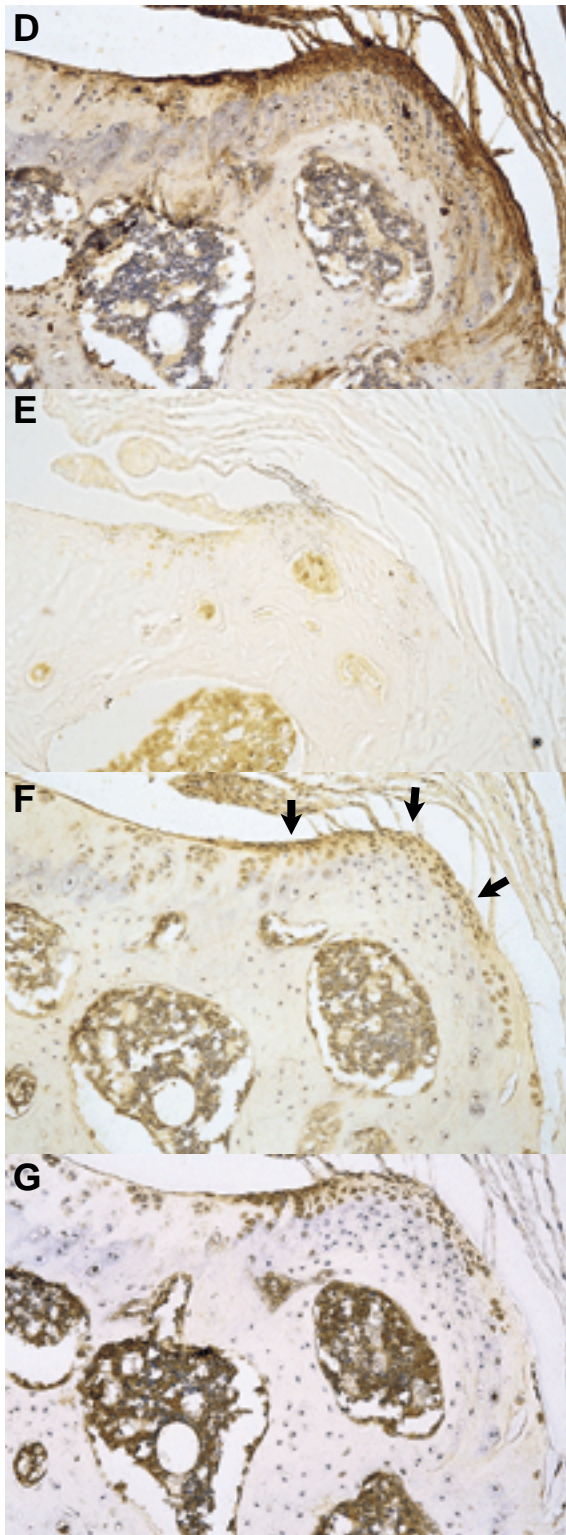


Fig. 4. Safranin-O (A) staining discloses the obvious formation of an osteophyte protruding from the articular margin in the severe group of 18-month-old animals with end-stage osteoarthritis. The osteophyte consists of type-I collagen (B), and hardly any chondrocytes and cartilage matrix positive for type-II collagen are observed (C). Fibrous connective tissue (arrows) is noted around the osteophyte, and IGF-1 (F) and IGF-1 receptor (G) are identified in the fibrous connective tissue. Fibroblastic-like cells in the fibrous connective tissue are positive for both type-I (B) and -III (D) collagens, and slightly positive for PCNA (E). JS, joint space; T, tibia. Original magnification: A, $\times 100$; B–G, $\times 200$.

[Figs. 4A–C on p. 138; Figs. 4D–G on p. 139]



Figs. 4D–G. *Continued from the previous page.*

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