J Orthop Sci (2004) 9:533–534
DOI 10.1007/s00776-004-0817-0

Journal of
Orthopaedic Science

Letter to the editor

Experimental models of osteonecrosis of the femoral head

To the editor

May 23, 2004

To explore the chain of events leading to osteonecrosis of the femoral head (OFH) of experimental animals, the models ought to replicate the "circulatory deprivation" disaster implied in the clinicians' practice of equating the epithets of "avascular" and "idiopathic" OFH. The reduced uptake of bone-seeking isotopes implicates disruption of the blood supply in triggering the diverse forms of nontraumatic OFH in humans. Regardless of whether the circulation is initially impeded at the level of the arteries, veins, capillaries, or sinusoids, in the end it is the arterial blood flow which is interrupted. Patients' avascular OFH may be idiopathic or incidental to one of a variety of diseases. Not so in experimental animals, in which the etiology, albeit not the pathogenesis, is finely tuned by the researcher.

Clinical trials of novel treatment modalities are hindered by the lack of appropriate experimental models of the human disease.[5] In other words, the ways and means by which investigators bring about the necrosis of the femoral head is a critical issue in validating trials to mimic clinical situations. Do the interventions, which truthfully represent experimental artifacts, thoroughly match the paradigm of etiological mechanisms at the bedside? As far as searches for optimal treatment modalities are concerned, the widely held belief in the effectiveness of therapeutically enhancing natural structural repair processes[3] is questionable at best. The mechanical properties of newly formed bone are inferior to those of those of mature, lamellar-fibered bone. Hence, the fast and extensive replacement of the subchondral osseous trabeculae during the early reparative stage by a disorganized, woven-fibered bone leads to early and severe femoral capital collapse incidental to everyday loads.[2]

Even nonskeptical readers have to acknowledge that, etiologically, a combined ischemic (vessel ligation) and cryogenic (liquid nitrogen) insult has little in common with human OFH, despite the fact that the researchers went all the way to get emus for their endeavors. True, the emus' femoral heads suffered necrosis,[3] but who would have thought otherwise? The authors' well-illustrated paper is a notable study in bone healing, but a kinship of their model to human OFH is dubious. Conzemius et al. assert antecedence for depicting a model in which there is progression to "human-like mechanical collapse".[3] Yet the emus' hips do not portray "end-stage" joint disease, i.e., disfigured femoral heads the surfaces of which segmentally lack cartilage, coupled with a fibrous pannus or a burnished and eburnated subchondral bony layer.[1]

A gamut of other articles describes experimental setups that are poorly designed to study human OFH. Of the reviewed models, we have fortuitously chosen an account of the destruction of piglets' capital femoral epiphyses 8 weeks after tightly placing a nonabsorbable ligature around the femoral necks. Radiographically, Kim and Su[4] have detected femoral capital flattening and fragmentation. Following revascularization of the ischemic necrotic bones, the predominant response is purportedly osteoclastic osteolysis with formation of large areas of resorption in the central region of the femoral heads. The authors stress the many osteoclasts congregating along revascularization fronts. Allegedly there is almost no appositional osteogenesis such that the resorbed bone is replaced by fibrovascular tissue. Where present, it is restricted to small foci in which revascularization is not followed by osteolysis and in which necrotic osseous trabeculae persist. The simultaneous presence of areas of osteogenesis and osteolysis may account for the radiographic impression of a fragmented femoral head.[4]

This correspondent has followed up (for 1 to 90 days) more than 400 rats with a vasculature-deprived femoral

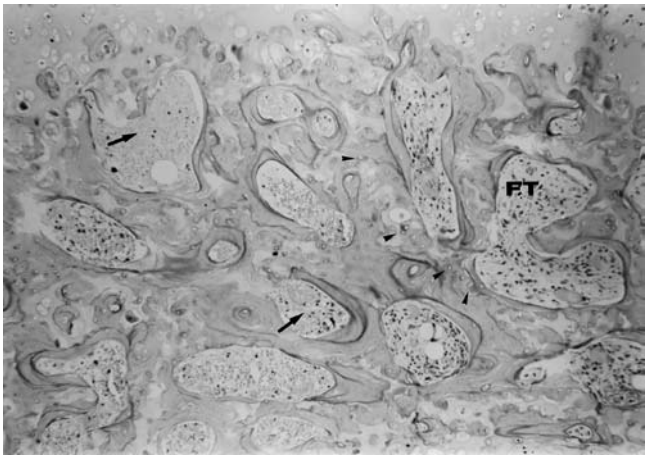

Fig. 1. Necrotic femoral head on the 6th day after surgically induced deprivation of the blood supply and blood drainage. The osteocytic lacunae in the epiphyseal trabeculae are optically empty (*arrowheads*), indicating cellular death. The marrow of the intertrabecular spaces consists of an eosinophilic and amorphous to granular substance lacking normal cell nuclei (expressing coagulation necrosis of the fatty-hematopoietic tissue of the marrow). Some karyopyknotic and karyorrhectic specks (*arrows*), constituting residues of the hematopoietic tissue, are randomly scattered within the amorphous material. On the *right side* of the illustration, there is the beginning of the ingrowth of fibrous tissue (*FT*) into the necrotic debris, a characteristic property of repair processes in the small laboratory animal. H&E, ×120. From reference 6, with permission

head, induced by cutting the cervical periosteum and ligamentum teres. The sine qua non for substantiating that a disastrous event has brought about a "bone infarct" (an earlier epithet for idiopathic osteonecrosis) is coagulation necrosis close in time to the operation, for instance, on or about the 5th day in rats. That is to say that the osteocytic lacunae are optically empty and the intertrabecular spaces are filled by amorphous or granular eosinophilic matter containing karyorrhectic and karyopyknotic speckles. As of the 2nd postoperative week, fibrous and granulation tissues centripetally advance from the (at this point in time) hyperplastic physeal–synovial junction into the necrotic epiphysis, incrementally permeating and resorbing the necrotic debris. The fibrous tissue carries with it undifferentiated mesenchymal cells, some of which differentiate into osteoblasts. The latter synthesize lamellar-fibered bone, which is appositionally deposited onto dead bony trabeculae, and woven-fibered intramembranous bone, which crisscrosses the intertrabecular spaces. There is a great deal of tissue turnover at this stage such that sites vacated in the wake of osteoclast-mediated osteolysis and chondroclast-mediated chondrolysis are shortly filled by newly formed osseous tissue. Consequently, the epiphysis consists of an immature, disorganized, and mechanically weak osseous framework that collapses under everyday loads. The joint cartilage exhibits loss of glycosaminoglycan and fibrillation and is focally destroyed, an eburnated and polished bone constituting the articular surface. These characteristics are the hallmarks of an osteoarthritis-like disorder.[1]

This correspondent submits that this chain of events and in the described order has to be realized in order to label an experimental setup a genuine analog of human femoral capital osteonecrosis.

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