

This Week's Citation Classic®

Mankin H J, Dorfman H, Lippiello L & Zarins A. Biochemical and metabolic abnormalities in articular cartilage from osteo-arthritic human hips. II. Correlation of morphology with biochemical and metabolic data. *J. Bone Joint Surg.—Amer. Vol. 53-A:523-37, 1971.* [Depts. Orthopaedics and Pathology, Hosp. Joint Diseases, Mt. Sinai Sch. Med., New York, NY]

Thirty-two areas of cartilage from nine osteoarthritic and four "normal" human femoral heads were studied morphologically and scored for "severity" of osteoarthrosis by a specially designed grading system. For each site, the concentrations of DNA and hexosamine and *in vitro* incorporation rates of ^3H -thymidine and ^{35}S O $_4$ were assessed. The data demonstrated that human osteoarthrosis is a highly focal disorder, that the proteoglycan concentration declines with advancing disease, and that a significant inverse relationship exists between synthetic activities and the severity of the process (strongly implying a "reparative" response). [The SCI® indicates that this paper has been cited in over 200 publications.]

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In the years 1966 to 1970, our Orthopaedic Biochemistry Laboratory at the Hospital for Joint Diseases in New York City was heavily engaged in research in the biochemistry of cartilage. During that period, Louis Lippiello, Antra Zarins, and I had been principally interested in chondrocyte metabolism but had had little opportunity to study the biochemical or metabolic features of osteoarthritic cartilage, chiefly because animal models were at the time considered not very useful, and human cartilage was difficult to obtain.

During that period, however, several members of the staff at the hospital began to do total hip replacements, and we suddenly found ourselves with not only a sizable amount of material to study, but an interested and talented pathologist, Howard Dorfman, to help us with the morphological analysis. After an initial effort to establish that the cartilage did in fact seem to have an increased metabolic activity,¹ we planned and carried out the study in about six months. Dorfman and I worked out the grading index and Lippiello, Zarins, and I did the chemistry. We also received a very helpful critique and some computational aid (these were the days before desktop computers) from Lawrence Rosenberg, at New York University, who was online with a statistical package!

It came as somewhat of a surprise to me that the article had been cited sufficiently to be declared a Citation Classic, not so much because of the work (which in the past 16 years has been substantiated and supported by a number of other observations), but because it's a little hard to believe that that many people are interested in osteoarthrosis! In any event, I believe that there are at least four reasons that the article has achieved this rather remarkable state of grace. First, the grading system that Dorfman and I devised is unique and has been used extensively by individuals who wish to quantitatively assess the severity of cartilage damage in osteoarthrosis (and other diseases) by a simple histological evaluation. Second, although not the first to do so, we clearly confirmed the remarkable degree of histological variation in osteoarthritic femoral heads and thus established the focal nature of the process. Third, by demonstrating that the rates of synthesis of DNA and proteoglycan varied inversely with the severity of the process, we established the fact that chondrocytes seemingly can respond to a stimulus (such as osteoarthrosis) and, perhaps more importantly, appear to be mounting a brisk reparative response. This allowed speculation as to the presence of an internal remodeling system now well established and very closely related to the synthesis and release of neutral protease and collagenase.² Finally, the work has served as a major stimulus to this and other laboratories (some rather desperately attempting to disprove it!) to engage in studies of chondrocyte metabolism in health and disease.^{3,4}

The study has materially aided all of our careers. I moved to the Massachusetts General Hospital (MGH) and Harvard the year following publication. In 1975 I received the Kappa Delta Award for Outstanding Orthopaedic Research from the American Academy of Orthopaedic Surgeons and in 1986, the Shands Award from the Orthopaedic Research Society, largely on the basis of this and related works. Dorfman first went to Baltimore (Sinai Hospital and Johns Hopkins), and after a very distinguished career, has recently moved to Albert Einstein Hospital as a professor of pathology and orthopaedics. Lippiello, stimulated by this and other efforts, went on to graduate school and then to work first at the MGH and Harvard with us and subsequently became professor of orthopaedics and biochemistry at the University of Nebraska. Zarins moved to Boston and headed our laboratory technical staff for several years before retiring.

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