LETTER TO THE EDITOR

To the Editor:

I would like to comment on articles on "Osteoarthritis and Skeletal Regeneration" in the March/April *Journal of Rehabilitation Research and Development* 2000;37(2), (http://www.vard.org/jour/00/37/2/conte372.htm).

This "Single-Topic Issue on Mechanobiology" reminded me of the lecture entitled "The Mechanogenesis of Osteoarthritis" I gave at the Massachusetts Institute of Technology on October 10, 1984 on the occasion of the tenth anniversary of the founding of the Whitaker Health Sciences Fund. The Fund was supported by Uncas A. Whitaker, MIT Class of 1923, founder of the AMP Corporation, who also endowed the Whitaker Chair I was privileged to occupy from 1974 until assuming my emeritus status in 1992. The early confidence in the potential of biomedical engineering by Uncas Whitaker, continued by his wife Helen and now by the Whitaker family, is epitomized by the dominant role the Whitaker Foundation has been playing in the financial support and encouragement of biomedical engineering research and programs.

This same issue of the *Journal of Rehabilitation Research and Development* also carries my "Letter to the Editor" (1) commenting on an earlier single-topic issue, this on low-vision and blindness (J Rehabil Res Dev 1999;36[4]; http://www.vard.org/jour/99/36/4/conte364.htm), the area which introduced me to rehabilitation engineering in the late 1950s.

Here my remarks focus on the articles by Wren et al. "Mechanobiology of tendon adaptation to compressive loading through fibrocartilaginous metaplasia" (J Rehabil Res Dev 2000;37(2):135–43), Beaupré et al. "Mechanobiology in the development, maintenance, and degeneration of articular cartilage" (J Rehabil Res Dev 2000;37(2):145–51), Smith et al. "Time-dependent effects of intermittent hydrostatic pressure on articular chrondrocyte type II collagen and aggrecan mRNA expression" (J Rehabil Res Dev 2000;37(2):153–61), and Andriacchi et al. "Methods for evaluating the progression of osteoarthritis" (J Rehabil Res Dev 2000;37(2):163–70).

The first three articles address changes in macroscopic and microscopic components of tendon and cartilage as a consequence of the loadings imposed on the tissue. Thus one would suppose the respective authors would employ relevant data on the pressures (loadings) the tissues experience in life. To my knowledge, the only such *in vivo* data has been telemetered from pressure-instrumented endoprostheses (2,3) congruently fitted to human acetabula (with all appropriate review board and subject consent) so as to replicate the geometry and maintain the musculature of the hip joint as it was prior to femoral head replacement. Eight cumulative years of longitudinal data have been acquired from two subjects, reporting dynamic pressures on articular cartilage, extending from post-surgical recovery through various acts of daily living, with synchronized kinematic and kinetic external measures of body-segment and whole-body activity. Data were reported initially in the *Proceedings of the National Academy of Sciences* (4), in a news report in *Science* (5), in the *Journal of Bone and Joint Surgery* (6), and in other journals, for example (7–11).

Wren et al. define an "Adaptation Rule" (Figure 2), relating tissue permeability to the "hydrostatic pressure stimulus f", which they apply in their finite element analysis to calculate the putative conversion of tendon into cartilage contingent upon a permeability change of 10^{-14} to 10^{-16} m^4/Ns.

To establish the value of the "minimum pressure needed to maintain cartilaginous tissue" for Figure 2, Wren et al. cite the PNAS (4) and JBJS (6) articles and say "... 2.5 MPa represents the lower end of physiologic cartilage pressures measured during normal activities of daily living." Nowhere in either of the cited articles or in any of our other publications or theses reporting *in vivo* pressure measurements have we ever described or defined a minimum pressure needed to maintain cartilaginous tissue. In fact the text and figures of the cited publications report many localized pressures on articular cartilage below 2.5 MPa.

Since the pressure value of the Adaptation Rule of Figure 2 is central to their analyses, Wren et al.'s conclusions on the causes of the metaplasia of tendon into cartilage are on uncertain grounds.

On page 41, Wren et al. note that "As we have shown in this study, such loading leads primarily to fluid pressurization with little fluid flow" and cite four other "theoretical analyses" which "also found that little fluid flow occurs in articular and epiphyseal cartilage during the short time associated with physiological loading." This is not surprising given the premises assumed in the theoretical analyses and the related experiments on excised cartilage discs (see Discussions of the two Atesian et al. articles [12,13]). In fact, this "little fluid flow" accounts for the remarkable load carriage, low friction, and longevity of the normal synovial joint! Over a lifetime, this repetitive flow may contribute to what is ultimately clinically diagnosed as primary osteoarthritis.

Macirowski's Sc.D. thesis (14) and subsequent article (15) describe an analytical-experimental study that quantified this "little fluid flow". *In situ* ultrasonic techniques applied to normal acetabula defined their geometry, permeability, and modulus values and distributions. Then FEM analyses iterated between measured joint consolidations under load and the corresponding measured pressure distributions using an *in vitro* version of the endoprosthesis. The study quantified (among other parameters) the velocity of the fluid flow normal to, and out of, the cartilage layer into the interarticular gap, and the low gap conductance which acts as an "interarticular seal". Macirowski's study confirmed the 1959 "weeping" hypothesis of McCutchen (16), but a simple thought experiment can develop the same qualitative result: Cartilage in the normal synovial joint is saturated with fluid. Loading not only pressurizes the fluid, but also strains (compresses) the cartilage matrix. When the saturated sponge (the cartilage matrix) is squeezed, incompressible fluid must be expressed, so some fluid flow into the gap must occur!

Subsequently, Tepic applied Macirowski's interarticular conductance data to the dynamic simulation of fluid flow in mating normal femoral head and acetabula, characterized by their respective cartilage geometries and constitutive properties (17). When loaded and articulated as in gait, Tepic's simulation describes the tangential interarticular flow, outward after heel-strike and reversing after toe-off, aligned with the split-line patterns seen on the cartilage (see Figure 5, reference 17). The necessary condition for the normal mechanical function of the synovial joint is shown to be an effective interarticular seal.

Wren et al. employed a "poroelastic model" (as did Macirowski), noting that "Poroelastic and biphasic models are equivalent when the fluid phase is inviscid, as is usually assumed." However, I would also like to see a reference to the original poroelastic formulation of Biot (18).

The analyses of Beaupré et al. and the experiments of Smith et al. assume cartilage pressure values, but the authors do not cite any of the *in vivo* articles in the references herein. Curiously, Smith et al. cite work from the Columbia University group (Smith et al.'s references 19–23) as defining "the magnitude and distribution of forces [did they mean pressures?] across joint surface"; none of these five references deal with whole joints or the forces or pressures they experience.

Beaupré et al. conduct a finite element model "of a simplified joint" to "provide further support for the view that mechanobiological factors play a key role in regulating the distribution of cartilage thickness and in maintaining a stable cartilage layer at maturity" and assert that "Osteoarthritis can be considered as the final stage in the process of endochrondral ossification during ontogeny"(citing as the basis for this last statement their own references 4–6).

That mechanobiological factors influence, if not control, the ossification of initially cartilaginous "bones", leaving the articular cartilage layers that constitute the synovial joint, is widely accepted. What "mechanobiological factor" accounts for this progression and then termination is debatable. Tepic is his Sc.D. thesis (19), starting with the diffusion equation, makes a convincing case that ossification is terminated and corresponding cartilage thickness distributions determined by strain penetration through the cartilage generated by daily loading of the joint.

However, I wish to focus on the Beaupré et al. premise that osteoarthritis "can be considered as the final stage in the process of endochrondral ossification" and from their "CONCLUSION": "...this study suggest(s) that primary or idiopathic OA is the final stage of skeletal ontogeny."

The Beaupré et al. analyses assume that the cartilage layer, however thin, maintains its integrity throughout the degeneration process, as characterized by their unchanging FEM parameters. However, the clinical sign of OA is fibrillation, as initially observed at the lamina splendens, which then progresses to crevassing deep into the layer. To quote a medical authority "Fibrillation should be accepted as a common microscopic end point of the many normal and abnormal factors that lead to cartilage failure" (20), or for a quote more quantitatively oriented "...the collagen fibres will rupture as the outer layers of the articular surfaces are subjected to excessively high shear stresses. The state, known as fibrillation, is often considered the first indication of the onset of arthrosis." (21) So, how can unchanging FEM parameters of Beaupré et al., which describe the cartilage as homogeneous and continuous, describe the degenerative process post fibrillation?

Returning to the thought experiment above, in the normal joint, the low conductance of the interarticular seal limits the escape of fluid from the pressurized areas to the joint capsule; the load is supported by hydrostatic fluid pressure, with the cartilage matrix experiencing average stresses of tenths of an MPa (see Figure 11 of reference 15). However, with fibrillation, increased interarticular leakage (and related reduced fluid pressurization and lowered fluid load carriage) occurs at every loading, putting the cartilage matrix at ever greater risk, which describes the downward spiral of clinical OA. This was evident in our ex-vivo study of one of our subject's acetabula cartilage, indicating the onset of low-grade OA in high pressure regions. (22)

Andriacchi et al. employ gait analysis "to calculate the external joint loading parameters directly related to the internal joint loads." The external and internal joint loadings are not "directly" related, as inverse Newtonian analyses cannot account for the co-contraction components of muscles active across a joint (23). Park et al. (24) compared, for a subject implanted with the pressure-measuring endoprosthesis, the location on the pseudofemoral head of the co-contraction-deficient Newtonian analysis with the location on the prosthesis of the highest local pressure that incorporates the co-contraction force components. As expected, the two locations were not co-located, and as movements required more co-contraction to enhance stability, such as when rising from a low chair, the mismatch increased.

Andriacchi et al.'s integration of external markers detectable by MRI, in conjunction with MRI images of the knee skeleton in static knee position, followed by dynamic gait analysis with the MRI detectable markers also recorded, provides a basis for evaluating the disjucture between the kinematics of skin-mounted markers and that of the internal skeletal segments, due to skin and soft tissue movement. Their cited references (Andriacchi et al.'s references 41–45) are from meeting proceedings and are therefore not very accessible. Fuller et al. (25) have demonstrated the sometimes considerable disjucture between external and internal kinematics through concurrent detection of external skin-mounted markers and similar markers mounted on bone pins inserted into the lower extremity segments of a human subject.

A final personal note. As one long convinced that the half of humanity of female gender is qualified to make scientific contributions beyond those so far in evidence, I find it gratifying that two of the articles in the issue are first-authored by women scientists, one a former student of mine at MIT and the other the daughter of an MIT faculty colleague.

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