

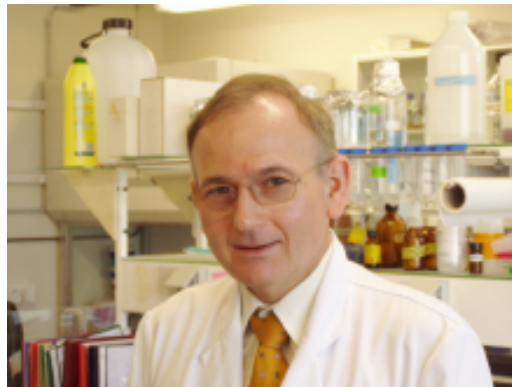
## CONNECTIVE TISSUE AND ARTHRITIS

**Daniel MANICOURT**, Member

**Hafida EL AJJAJI**, Postgraduate

**Annette MARCELIS**, Technician

**Anne van EGEREN**, Technician



*Among the many rheumatic disorders, the osteoarthritic diseases (OA) are the most prevalent disorders of the joint, with radiographic evidence seen in at least 70 % of the population over 65 years of age. OA is a group of overlapping distinct diseases, which may have different etiologies but with similar biologic, morphologic, and clinical outcomes. The disease processes not only affect the articular cartilage but involve the entire joint, including the subchondral bone, ligaments, capsule, synovial membrane, and periarticular muscles.*

### **Effects of nonsteroidal anti-inflammatory drugs on the overall metabolism of articular cartilage**

Because they inhibit cyclo-oxygenase (COX), and hence the production of prostaglandins (PGs), non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed to patients suffering from arthritis. Two isoforms of COX have been identified thus far: COX-1, which is constitutively expressed in most tissues and COX-2, which is highly inducible in response to proinflammatory cytokines and mitogens. It is generally believed that the beneficial effects of NSAIDs are related to their ability to inhibit COX-2 whereas the gastrointestinal and renal toxicity of these drugs results from their inhibition of COX-1, a contention that has provided the basis for the development of highly selective COX-2 inhibitors. It should be however stressed that COX-1-derived PGs can contribute to the inflammatory response and that COX-2-derived PGs perform physiologically important roles such as the maintenance of normal renal function. Furthermore, COX-2-derived PGs, in addition to their anti-inflammatory properties, have been implicated in the protection of the gastrointestinal tract from injury.

Although NSAIDs undeniably produce relief of pain and improvement of joint mobility in patients suffering from arthritis, *ex vivo* and *in vivo* studies have shown that some NSAIDs inhibit the synthesis of cartilage proteoglycans whereas others do not. This differential effect of NSAIDs on cartilage metabolism is most relevant to clinical practice since any drug, that suppresses proteoglycan synthesis and impairs the chondrocyte to repair its already damaged extracellular matrix, could potentially accelerate the breakdown of the cartilage tissue. On the other hand, although hyaluronan (HA) plays a central structural role in the supramolecular organization of proteoglycans and, hence on the biomechanical properties of articular cartilage, the possible effects of NSAIDs on the metabolism of this glycosaminoglycan has so far focused little investigative attention (1, 2).

We therefore investigated the action of celecoxib (a strong selective COX-2 inhibitor) on the metabolism of newly synthesized HA and proteoglycan molecules in explants from human OA cartilage (3). In contrast to classical NSAIDs, this COX-2 selective inhibitor had a positive effect on the overall metabolism of both proteoglycans and hyaluronan, two major components of the extracellular matrix of cartilage. This effect, which is independent of the inhibition of prostaglandin production, is under investigation as it might be of

great biological and therapeutic significance in arthritis.

### **Markers of connective tissue metabolism in health and disease**

*In collaboration with E. Thonar, Rush-Presbyterian-St Luke's Medical Center, Chicago, USA.*

Nowadays, several biochemical molecules derived from the joint components can be quantified in body fluids (joint fluid, blood and urine) (4 – 7). These molecules termed “metabolic markers” or simply “markers” appear as important tools to disclose *in vivo* important changes occurring during both the preclinical and clinical stages of various joint diseases, including osteoarthritis (6, 7). There is also evidence that these markers may prove helpful in determining whether a therapeutic regimen is effective or not, and this in a relatively short period of time (5, 6). Indeed, in the absence of markers, the efficacy of treatment in joint disorders relies mainly on radiographic changes, an approach that takes years before one can reach meaningful results.

The markers that are most currently used are hyaluronan, a marker of synovial proliferation and inflammation, antigenic keratan sulfate, a marker of proteoglycan metabolism, cartilage oligo-matrix protein, a marker of cartilage matrix remodeling, and the telopeptides of type II collagen, a marker of the breakdown of cartilage collagen (6). There is indeed good agreement that this panel of markers helps diagnose, monitor or prognosticate osteoarthritic changes.

### **Role of the subchondral bone in the initiation and progression of the osteoarthritic disease process**

So far, the possible role of subchondral bone in the initiation and/or progression of osteoarthritis (OA) has focused little investigative attention. We have therefore explored this topic in an animal model of osteoarthritis. In this model, severing of the anterior cruciate ligament of the knee increases dramatically the biomechanical forces applied to the internal compartment of the knee joint and results in the progressive apparition of OA lesions in the operated joint which closely resemble those seen in human OA.

During the first weeks following joint destabilisation, we have observed a dramatic decrease in the density and volume of the trabecular subchondral bone. These changes increased with time post-surgery and were restricted to the internal

compartment of the operated joint whereas no significant changes in bone density and volume could be disclosed in the external compartment of the unstable joint.

Obviously, these changes reflect an adaptation of the bone to absorb the enhanced biomechanical forces imposed upon it. On the other hand, these changes concomitantly induce a dramatic increase in the tensile and shearing forces upon the overlying articular cartilage and, in so doing, contribute to the degradation of the cartilage tissue. Our working hypothesis is supported by the finding that animals receiving drugs known to inhibit bone resorption do not show up any change in the volume and density of the trabecular subchondral bone of the operated knee and, more importantly, exhibit a dramatic decrease in the severity of cartilage OA lesions (8).

These findings open a new approach in the therapeutic regimen of OA and studies are currently conducted in human OA. Results of the preliminary clinical trial will be known during the year 2003.

### **Towards a better understanding of the metabolism of hyaluronan in connective tissues**

Research efforts are also devoted to the regulation of hyaluronan metabolism both in health and disease. In the skin, which contains 50 % of total body hyaluronan, the half-life of hyaluronan is about one day, and even in as seemingly inert tissue as cartilage, hyaluronan turns over with a half-life of one to three weeks. In the blood stream, the half-life of hyaluronan is two to five minutes. All such catabolism is presumably a result of hyaluronidases. What is the nature of the control mechanisms that orchestrate such vastly different rates of turnover? The hyaluronan of vertebrate organisms can exist in many states, in a variety of sizes, in extracellular forms, free in the circulation, loosely associated with cells and tissues, tightly intercalated within proteoglycan-rich matrices such as that of cartilage, bound by receptors to cell surfaces, or even in several intracellular locations. Superimposed on these many states are the panoply of binding proteins, or hyaladherins, that decorate the hyaluronan molecule. How do mechanisms of catalysis differ among this wide range of physical and chemical states of the hyaluronan substrate? It is unlikely that hyaluronidase activity is retained *in vivo* in an active form within the extracellular matrix where it could cause great havoc. If it is found within the extracellular matrix, it may be in an inactive or suppressed form, perhaps bound to an inhibitor. Such a situation would parallel the relationship between the metalloproteinases and the tissue inhibitors of metalloproteinases or TIMPs

that exert exquisite control over metalloproteinase activity.

### Selected publications

1. Manicourt DH, Druetz-Van Egeren A, Haazen L, Nagant de Deuxchaisnes C. *Effects of tenoxicam and aspirin on the metabolism of proteoglycans and hyaluronan in normal and osteoarthritic human articular cartilage.* **Br J Pharmacol** 1994;113: 1113-20.
2. Blot L, Marcelis A, Devogelaer JP, Manicourt DH. *Effects of diclofenac, aceclofenac and meloxicam on the metabolism of proteoglycans and hyaluronan in osteoarthritic human cartilage.* **Br J Pharmacol** 2000;131: 1413-21.
3. El Hajjaji H., Marcelis, A., Devogelaer, and J-P. And Manicourt, D-H *Celecoxib has a positive effect on the metabolism of proteoglycans and hyaluronan in human osteoarthritic cartilage.* **J Rheumatol**, In press.
4. Manicourt DH, Poilvache P, Van Egeren A, Devogelaer JP, Lenz ME, Thonar EJ. *Synovial fluid levels of tumor necrosis factor alpha and oncostatin M correlate with levels of markers of the degradation of crosslinked collagen and cartilage aggrecan in rheumatoid arthritis but not in osteoarthritis.* **Arthritis Rheum** 2000;43: 281-8.
5. Manicourt DH, Poilvache P, Nzeusseu A, van Egeren A, Devogelaer JP, Lenz ME, Thonar EJ. *Serum levels of hyaluronan, antigenic keratan sulfate, matrix metalloproteinase 3, and tissue inhibitor of metalloproteinases 1 change predictably in rheumatoid arthritis patients who have begun activity after a night of bed rest.* **Arthritis Rheum** 1999;42: 1861-9.
6. Thonar E. J.M., Lenz M.E., Masuda K. and Manicourt D.H. : *Body fluid markers of cartilage metabolism.* In **Dynamics of bone and cartilage metabolism.** ( M.J. Seibel, S. P. Robins and J. P. Bilezikian, eds) Academic Press, San Diego, pp 453-64, 1999
7. Manicourt D. H., El Hajjaji H., Devogelaer J. P. and Thonar E. J.M : *Products of cartilage metabolism.* In **Dynamics of bone and cartilage metabolism.** ( M.J. Seibel, S. P. Robins and J. P. Bilezikian, eds) Academic Press, San Diego, pp 301-317, 1999
8. Manicourt DH, Altman RD, Williams JM, Devogelaer JP, Druetz-Van Egeren A, Lenz ME, Pietryla D, Thonar EJ. *Treatment with calcitonin suppresses the responses of bone, cartilage, and synovium in the early stages of canine experimental osteoarthritis and significantly reduces the severity of the cartilage lesions.* **Arthritis Rheum** 1999;42:1159-67.