

## W O N D E R   W H Y ?

# The Acceleration of Articular Cartilage Degeneration in Osteoarthritis by Nonsteroidal Anti-inflammatory Drugs

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## ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world for the treatment of osteoarthritis (OA) symptoms, and are taken by 20-30% of elderly people in developed countries. Because of the potential for significant side effects of these medications on the liver, stomach, gastrointestinal tract and heart, including death, treatment guidelines advise against their long term use to treat OA. One of the best documented but lesser known long-term side effects of NSAIDs is their negative impact on articular cartilage.

In the normal joint, there is a balance between the continuous process of cartilage matrix degradation and repair. In OA, there is a disruption of the homeostatic state and the catabolic (breakdown) processes of chondrocytes. It is clear from the scientific literature that NSAIDs from in vitro and in vivo studies in both animals and humans have a significantly negative effect on cartilage matrix which causes an acceleration of the deterioration of articular cartilage in osteoarthritic joints. The preponderance of evidence shows that NSAIDs have no beneficial effect on articular cartilage in OA and accelerate the very disease for which they are most often used and prescribed. Some of the effects of NSAIDs on the articular cartilage in OA include inhibition of chondrocyte proliferation, synthesis of cellular matrix components, glycosaminoglycan synthesis, collagen synthesis and proteoglycan synthesis. The net effect of all or some of the above is an acceleration of articular cartilage breakdown.

In human studies, NSAIDs have been shown to accelerate the radiographic progression of OA of the knee and hip. For those using NSAIDs compared to the patients who do not use them, joint replacements occur earlier and more quickly and frequently. The author notes that massive NSAID use in osteoarthritic patients since their

introduction over the past forty years is one of the main causes of the rapid rise in the need for hip and knee replacements, both now and in the future.

While it is admirable for the various consensus and rheumatology organizations to educate doctors and the lay public about the necessity to limit NSAID use in OA, the author recommends that the following warning label be on each NSAID bottle:

**The use of this nonsteroidal anti-inflammatory medication has been shown in scientific studies to accelerate the articular cartilage breakdown in osteoarthritis. Use of this product poses a significant risk in accelerating osteoarthritis joint breakdown. Anyone using this product for the pain of osteoarthritis should be under a doctor's care and the use of this product should be with the very lowest dosage and for the shortest duration of time.**

If NSAID use continues, then most likely the exponential rise in degenerative arthritis and subsequent musculoskeletal surgeries, including knee and hip replacements as well as spine surgeries, will continue to rise as well.

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**KEYWORDS:** accelerating articular cartilage degeneration, articular cartilage, cox-2 inhibition, non-steroidal anti-inflammatory medication, NSAID, osteoarthritis, prostaglandin.

**N**onsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world for the treatment of osteoarthritis (OA) symptoms,<sup>1</sup> and are taken by 20-30% of elderly people (defined as people over the age of 64 years) in developed countries.<sup>2</sup> The worldwide pain management prescription drug market totaled approximately \$24 billion in 2002 and passed \$30 billion by 2006. Celebrex (celecoxib) led the pack with nearly \$4 billion in sales in 2002.<sup>3</sup> Each year,

over 70 million prescriptions for NSAIDs are dispensed in the United States, 20 million in Great Britain and 10 million in Canada.<sup>4,6</sup> These numbers do not include the 30 billion over-the-counter tablets sold each year in the United States alone.<sup>7,8</sup> The most common over-the-counter and prescription nonsteroidal anti-inflammatory drugs are seen in *Figure 1*.

- Aspirin (Bayer)
- Celecoxib (Celebrex)
- Diclofenac (Voltaren)
- Etodolac (Lodine)
- Fenoprefen (Nalfon)
- Ibuprofen (Advil, Motrin)
- Indomethacin (Iddocin)
- Keopropfen (Orudis, Oruvail)
- Ketoralac (Toradol)
- Nabumetone (Relafen)
- Naproxen (Aleve)
- Oxaprozin (Daypro)
- Salsalate (Disalcid)
- Sulindac (Clinoril)
- Tolmetin (Tolectin)

**Figure 1. Common over-the-counter and prescription nonsteroidal anti-inflammatory drugs (NSAIDs).**

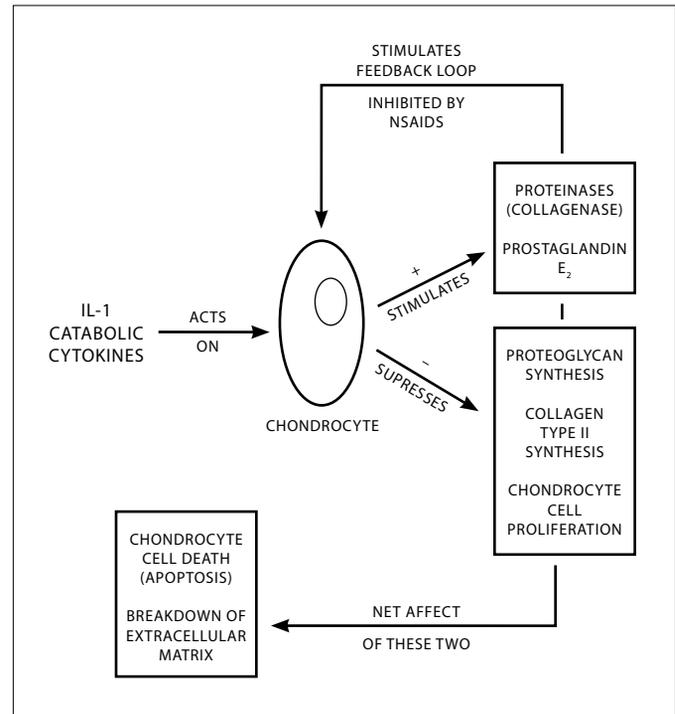
Treatment guidelines in the United States, Great Britain, and Canada recommend NSAIDs as second-line treatment (after acetaminophen) for mild OA and as first-line treatment for moderate to severe OA.<sup>9-11</sup> As baby boomers age, it is estimated that the number of NSAID users will continue to climb, despite the fact that over 100,000 people are hospitalized for gastrointestinal bleeding and of those 16,500 people die from NSAID toxicity each year.<sup>12,13</sup> In 2006, the Osteoarthritis Research Society International formed an international committee to review all guidelines and evidence available on OA. Based on the evidence of potentially serious adverse reactions to NSAIDs, the committee has advised against the long-term use of NSAIDs to treat OA.<sup>14</sup> One of the most serious adverse reactions to NSAIDs, that is little appreciated, is that as a class of compounds they cause the breakdown of articular cartilage, thereby accelerating OA, the very disease for which they are most commonly prescribed.

In the normal joint, there is a balance between the continuous process of cartilage matrix degradation and repair. In OA, disruption of the homeostatic state occurs and the catabolic (breakdown) processes of chondrocytes are increased. The principal cytokines linked to the catabolism of cartilage and to the OA process are interleukin (IL)-1, tumor necrosis factor (TNF)- $\alpha$ , and IL-6. IL-1 is the prototypic inducer of catabolic responses in chondrocytes. This substance causes the increased secretion of proteinases (which

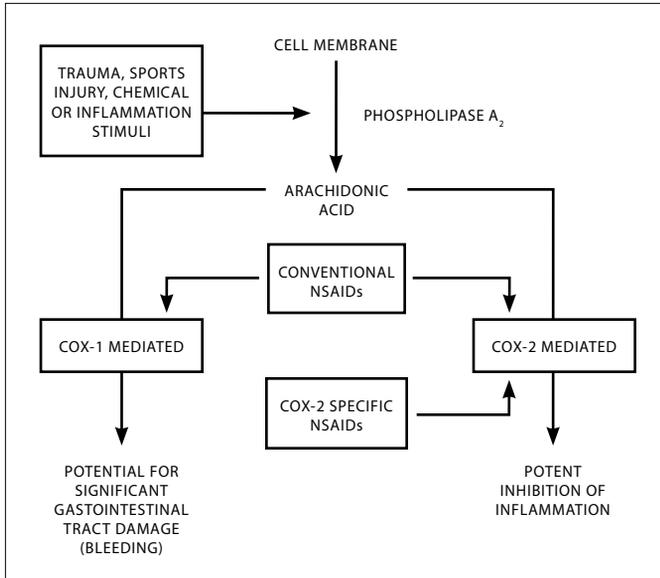
breakdown cartilage matrix) including collagenase, the suppression of proteoglycan synthesis leading to the suppression of matrix synthesis, and ultimately the reduction of the number of chondrocytes.<sup>15, 16</sup> (See *Figure 2*.) IL-1 is a potent inducer of prostaglandin (PG) synthesis by inducing PGE<sub>2</sub> synthesis in human chondrocytes. The rate-limiting step for the synthesis of PGE<sub>2</sub> and other prostaglandins is the conversion of arachidonic acid to prostaglandin endoperoxide by cyclooxygenase (COX), which exists in two isoforms, COX-1 and COX-2. All NSAIDs inhibit both COX 1 and 2 enzymes but most of the NSAIDs that have been developed in recent years show greater activity of COX 2 in order to decrease gastrointestinal side effects. (See *Figure 3*.) PGs act (among other things) as messenger molecules in the process of

**Chondrocytes** – the only cells in cartilage tissue responsible for the synthesis of collagen and proteoglycans that makeup the cartilage matrix.

**Cytokines** are signaling molecules used extensively in cellular communications.



**Figure 2. The catabolic physiology leading to articular cartilage breakdown.** Interleukin-1 is one of the principle cytokines that initiates a cascade that leads to chondrocyte cell death and extracellular matrix breakdown. NSAIDs inhibit prostaglandins, such as PGE<sub>2</sub>, from stimulating chondrocyte DNA matrix synthesis thereby contributing to articular cartilage degeneration.



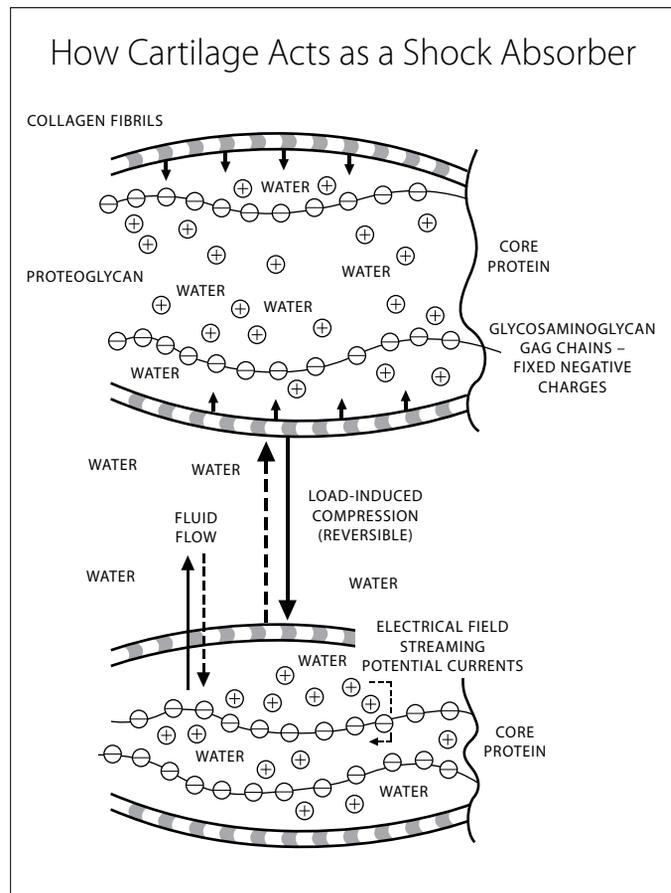
**Figure 3. Inhibition of cyclooxygenase 1 and 2 by NSAIDs.** Studies have shown that, although most NSAIDs inhibit both COX-1 and COX-2, it is the inhibition of COX-2 that is responsible for the anti-inflammatory effects of NSAIDs. On the other hand, inhibition of COX-1 by these agents causes damage to the GI tract. This has led to the development of a new generation of NSAIDs that specifically inhibit COX-2.

inflammation. It was hoped that the use of NSAIDs would decrease the catabolic program in OA, thereby having a disease-modifying effect. Research, unfortunately is showing PGs, like PGE<sub>2</sub>, stimulate chondrocyte proliferation and subsequent synthesis of cellular matrix components.<sup>17</sup> The net result of their blockade and other NSAID effects is the acceleration of articular cartilage degeneration. To show how this occurs and to what extent, a basic understanding of articular cartilage anatomy is needed.

ARTICULAR CARTILAGE ANATOMY

Articular cartilage functions as a wear-resistant, smooth, nearly frictionless, load-bearing surface. The composition and physiochemical properties of articular cartilage, the fundamental organization of the collagen network, and the molecular organization of collagen and proteoglycans all have profound effects on the intrinsic mechanical properties of the extracellular matrix.<sup>18</sup> Cartilage is composed of a complex extracellular matrix of collagen and elastic fibers within a hydrated gel of glycosaminoglycans and proteoglycans. This extracellular matrix, which makes up 98% of the articular cartilage volume, is synthesized by the chondrocytes which comprise the other 2% of the cartilage tissue. It is well known that chondrocytes can synthesize the extracellular matrix such

as proteoglycans, collagen, fibronectin, integrins, and other adhesive proteins which are needed to maintain the high tensile strength and low compressibility under load of the articular cartilage.<sup>19, 20</sup> Type II collagen is the predominant collagen type in the extracellular matrix with proteoglycan (PRG) macromolecules dispersed throughout. They contain highly negatively charged carboxyl and sulfate groups (keratin and chondroitin sulfate) on the glycosaminoglycans, giving them a high affinity for water. (See Figure 4.) The nature of the high density of negative charges imparts the physical properties to PRGs. Because of their attraction and binding of water, PRGs are viscous, making them ideal for lubricating fluid in joints. The charges repel each other, which gives them an open structure and is space-filling. These biochemical traits contribute to the mechanical properties of PRGs in articular cartilage, such as absorption and distribution of compressive weight, protecting structures in the joints from mechanical damage.<sup>21</sup> The normal synthesis and breakdown of the PRGs and their component molecules,



**Figure 4. The proteoglycan structure of articular cartilage.** The high content of water in proteoglycans help the cartilage act as a shock absorber.

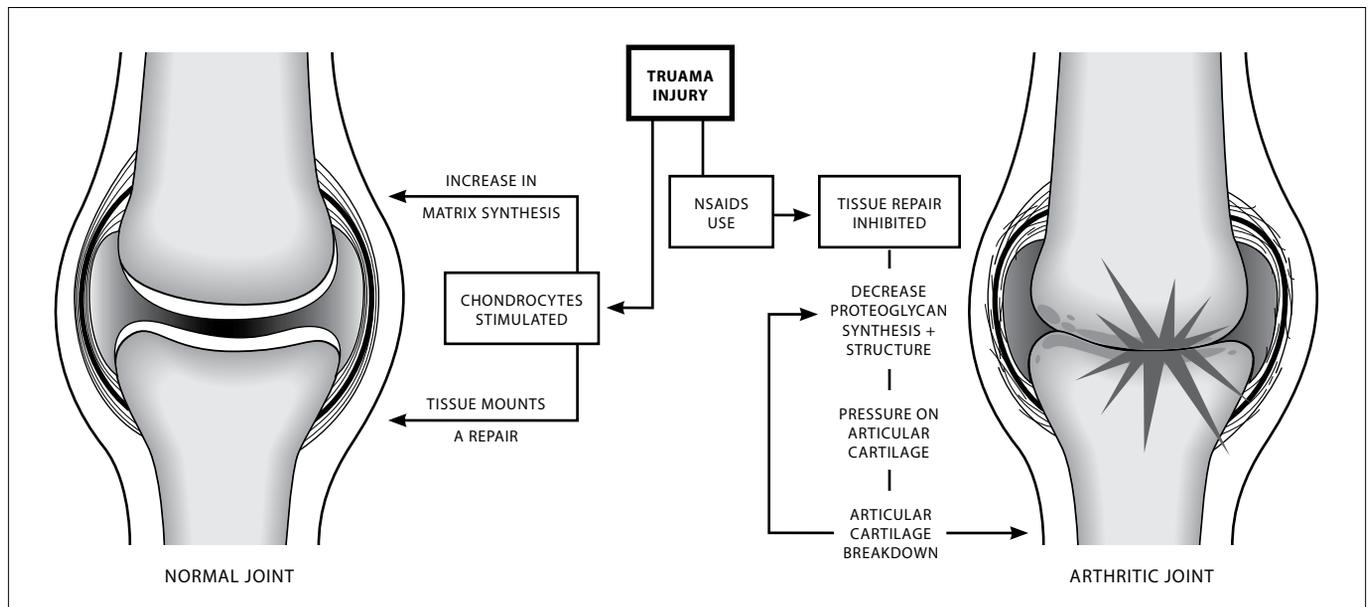
including glycosaminoglycans, is mediated by the indigenous chondrocytes. Glycosaminoglycans turn over several times as rapidly as the fibrillar collagen. If any part of this complex system is disrupted, the normal properties of articular cartilage are jeopardized, leading to joint degeneration. It is the extracellular matrix of articular cartilage that is the primary target of osteoarthritic cartilage degeneration and the accelerating effects of this breakdown by NSAIDs.

One of the earliest features of the development of osteoarthritis is degeneration of the articulating surfaces of the joint. This is characterized by fibrillation of the articular cartilage, in which the mesh of collagen fibers is disrupted. Degeneration of type II collagen is seen, as well as a decrease in the extracellular matrix.<sup>22</sup> Loss of proteoglycan from the matrix is characteristic. The loss of aggrecan, the predominant PRG in articular cartilage imposes an increasing load on the collagen fibrils, causing further breakdown.<sup>23</sup> Early in the course of OA, the tissue mounts an attempt at repair. Chondrocytes proliferate and there is an increase in matrix synthesis.<sup>24</sup> However, if this repair process is disrupted for any reason including the use of NSAIDs, degradative enzymes overwhelm the synthetic capability and the repair fails. Particular compositional, molecular, and structural changes will continue to occur within the articular cartilage including decreased proteoglycan and increased water content, collagen fibril network disorganization, and proteoglycan

separation, as long as the inciting issue (NSAID use) continues. (See Figure 5.) These changes alter the intrinsic mechanical properties of articular cartilage and produce swelling.<sup>25</sup> The articular cartilage, having lost some of its compressive ability under load, further degenerates. As the surface fibrillation progresses, the articular defects penetrate deeper into the cartilage until the cartilage is lost. The increased pressure on the subchondral bone causes it to thicken. Often bone cysts form deep to the eburnated areas. Eventually, bony nodules or osteophytes form at the periphery of the cartilage surface. All of these changes account not only for the pathology found on radiographs or histologically (findings under the microscope), but also for the joint pain, tenderness, loss of motion and stiffness of OA.<sup>26</sup> It is the relief of some of these clinical manifestations that accounts for the widespread use of NSAIDs not only in the United States, but around the world.

THE EXTENT OF THE PROBLEM

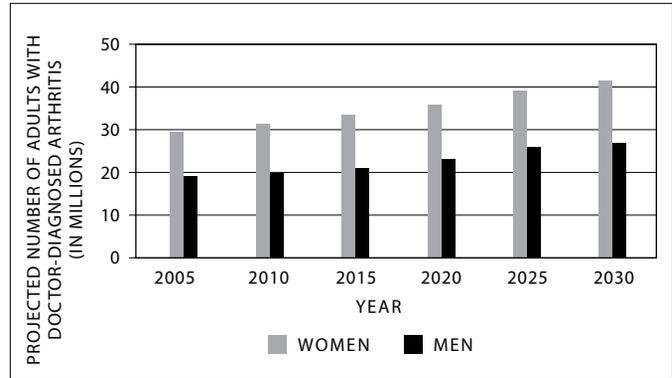
In 2006, the Center for Disease Control combined data from the National Health Interview Survey years 2003-2005 Sample Adult Core components to estimate the average annual arthritis prevalence in the U.S. population aged 18 years and older. Overall, 21.6% (46.4 million) of adults reported arthritis or another rheumatic condition diagnosed by a doctor, with 27 million Americans having osteoarthritis, up from 21 million in 1990.<sup>27, 28</sup> By the year



**Figure 5. The pathogenesis of osteoarthritis accelerated by NSAIDs.** NSAID use inhibits the body's repair processes, leading to decreased proteoglycan and extracellular matrix content and function, which ultimately leads to articular cartilage breakdown.

2030, an estimated 67 million (25% of the projected total adult population) adults aged 18 years and older will have doctor-diagnosed arthritis with two-thirds of those with arthritis being women. (See Figure 6.) The impact of this arthritis on individuals is significant. Almost 41% report severe limitations in their usual activities and 31% report being limited in work due to the arthritis.<sup>29</sup> (See Figure 7.) The average direct cost (medications, assistive devices) of OA is approximately \$2,600 per year per person living with OA, but the total annual cost (including lost wages, loss of productivity) of OA per person living with OA is at the low end \$5,700 but in the high end over \$10,000.<sup>30-32</sup> The question remains as to why is there this alarming increase in osteoarthritis to the point that between 1997 and 2005 the number of knee surgeries climbed by 69% from 328,800 to 555,800, hip replacements rose 32% from 290,700 to 383,500, and spinal fusion surgeries increased by 73% from 202,100 procedures to 349,400 per year?<sup>33</sup>

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used classes of medications. Ibuprofen was the first NSAID available by prescription in the United States in 1974, under the brand names Motrin and Rufen. It rose to be the fifth-largest selling prescription drug and in 1984 was the first new entrant in the non-prescription pain reliever market in nearly 30 years. For the last thirty plus years, NSAIDs are among the most frequently used drugs in the United States. From 1973 to 1983, for instance, the number of NSAID prescriptions dispensed by retail pharmacies tripled, rising from 28 million to around 70 million by the early 1980s. (See Figure 8.) What are the long-term effects of this NSAID use? Could it be that the massive widespread use of NSAID twenty and thirty plus years ago is the reason that there is currently an epidemic of disabling osteoarthritis resulting in a slew of spine and joint replacement operations? By 1983, five of the 50 drug products most often dispensed were NSAIDs, representing over 4% of the total prescription market.<sup>34</sup> To put a practical visual on these numbers in percentage terms, enough NSAIDs were purchased in the United States by drugstores and hospitals to treat 1.29% of the entire civilian population each day in 1983. The number one use for these NSAIDs in 1983 was osteoarthritis. While the prescribing patterns for specific NSAIDs have changed over the years, as drugs like ibuprofen and naproxen became available over-the-counter, an NSAID is still the number one medication

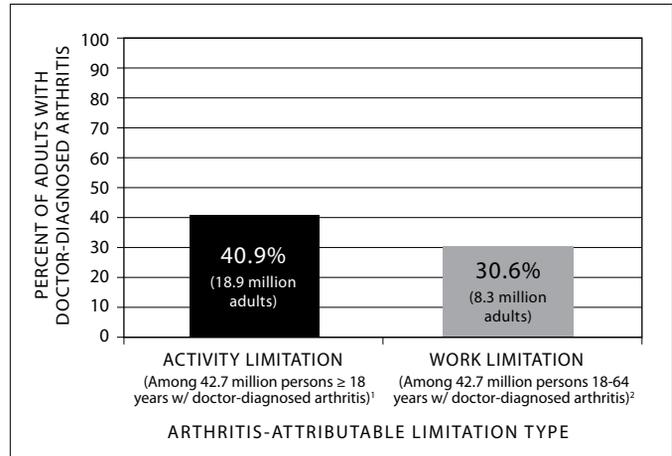


**Figure 6. Projected prevalence of doctor-diagnosed arthritis, in US adults 18 and older, 2005-2030.**

Data Source: www.cdc.gov

Hootman JM, et al. Projections of U.S. prevalence of arthritis and associated activity limitations. *Arthritis Rheum.* 2006;54(1):226-229.

Hootman J, et al. Prevalence of doctor-diagnosed arthritis and arthritis-attributed activity limitation—United States, 2003-2005. *MMWR.* 2006;55(40):1089-1092.



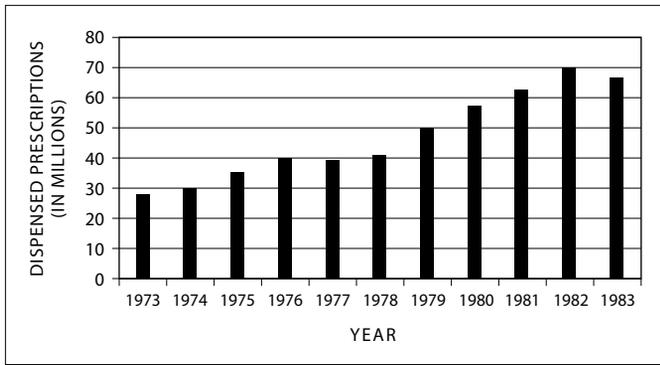
**Figure 7. Percent of adults with doctor-diagnosed arthritis with "arthritis attributable" activity and work limitations in 2002.**

Data Source: www.cdc.gov, 2002 National Health Interview Survey.

Hootman J, et al. Prevalence of doctor-diagnosed arthritis and arthritis-attributed activity limitation—United States, 2003-2005. *MMWR.* 2006;55(40):1089-1092.

Bolen J, et al. Racial/Ethnic differences in the prevalence and impact of doctor-diagnosed arthritis—United States, 2002. *MMWR.* 2005;54(5):119-123.

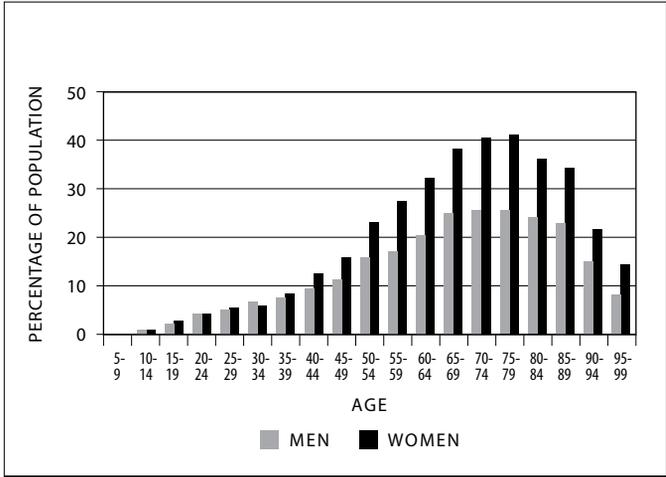
prescribed by physicians for osteoarthritis. For instance, 80% of rheumatologists noted they frequently prescribe NSAIDs for symptomatic hip and knee osteoarthritis, while for the same group of clients, 65% of primary care physicians use an NSAID.<sup>35, 36</sup> Even when physicians were educated on guidelines based on the European League Against Rheumatism, American College of Rheumatology, and The Arthritis Society guidelines for OA treatment,



**Figure 8. Prescriptions for nonsteroidal antiinflammatory drugs dispensed by retail pharmacies from 1973-1983.** Is it this widespread use of NSAIDs many years ago that has led to the current epidemic of disabling osteoarthritis?

limiting NSAID use, NSAIDs were still prescribed over half the time for patients with knee OA.<sup>37</sup> These prescribing patterns are confirmed in the numbers. For instance, in 2002, the prescriptions for generic ibuprofen and naproxen exceeded 500 million per year, with over 45 million prescriptions written for cyclooxygenase-2 (COX-2) inhibitors.<sup>38</sup> Realize, these numbers do not include all of the over-the-counter NSAIDs that have been consumed over the last thirty plus years. According to the National Consumers League survey conducted in 2002 on the public's use of and attitudes toward NSAID medications, 83% of the respondents had used an over-the-counter pain medication, with 15% using it daily.<sup>39</sup> When this survey was combined with The Roper National Survey of the over-the-counter pain reliever users, 38% used both prescription and over-the-counter pain relievers, and 44% consumed greater than the recommended dosages. The average length of the prescription drug use was 6.6 years.<sup>40</sup> In respondents who had arthritis pain, 85% used over-the-counter pain relievers. What this data means is that 36 million Americans are using over-the-counter pain medications daily, with roughly 23 million using NSAIDs. Other surveys have confirmed that a high percentage of the U.S. population (17% or greater) routinely uses over-the-counter NSAID medications.<sup>41, 42</sup> In a study of 2433 patients attending an outpatient physical therapy unit, 79% reported using either over-the-counter or prescription anti-inflammatory pain medication during the week prior to the survey.<sup>43</sup> In data that we have published concerning unresponsive neck, knee, hip, and temporomandibular joint pain, the average person experienced pain for over five years and was taking one or more pain medications at the time of their first Prolotherapy visit.<sup>44-47</sup> This epidemic NSAID prescribing

and consuming for osteoarthritis is seen in most developed countries where 20-30% of elderly people (age>64 years) with up to 40% of some populations receiving NSAIDs.<sup>48, 49</sup> (See Figure 9.) The question begs to be asked, "Could the use of these NSAIDs be the cause of the incredible rise of osteoarthritis and need for subsequent musculoskeletal surgeries, such as knee and hip joint replacements?"



**Figure 9. NSAID use according to age.** In some populations, especially among the elderly, over 30% are regularly using NSAIDs.  
Source: Chiroli S, et al. Utilisation pattern of nonspecific nonsteroidal anti-inflammatory drugs and COX-2 inhibitors in a local health service unit in northeast Italy, 2003. *Clin Drug Invest.* 23(11):751-760. © 2003 Adis Data Information BV.

THE ANIMAL DATA ON NSAIDS ACCELERATING CARTILAGE DETERIORATION

From observations in animal models of OA there is substantial evidence that NSAIDs are toxic to articular cartilage. Drs. Marshall J. Palmoski and Kenneth D. Brandt from the Indiana University School of Medicine published several research papers showing that NSAIDs suppress chondrocyte proteoglycan (PRG) synthesis. Prior to these studies they had already shown that salicylate (aspirin), the drug most commonly employed in the treatment of OA at the time, reduced PRG synthesis in cultures of normal articular cartilage by about 30% and in cultures of OA cartilage by up to 99% at levels achieved in the serum of patients treated with salicylate.<sup>50</sup> They also showed that salicylate (aspirin) accelerated the development of structure damage in the OA joint in the canine cruciate-deficient model or that caused by immobilization, and resulted in more severe pathology than that seen in the OA knees of dogs not treated with the drug.<sup>51-53</sup> As more clinicians started using ibuprofen

and other NSAIDs, instead of aspirin for OA, Drs. Palmoski and Brandt studied the effects these drugs had on canine articular cartilage. Specifically they found that fenopfen and ibuprofen inhibited net PRG synthesis in a concentration-dependent fashion. At concentrations in the culture medium comparable to plasma concentrations seen in patients after oral administration of NSAIDs in humans, net PRG synthesis in the presence of these drugs averaged 72% and 86% of the control values, respectively ( $P < 0.01$ ).<sup>54-56</sup> (See Figure 10.)

In another study on canine articular cartilage, these researchers found that the inhibitory effect of the NSAID indomethacin was greater when the articular cartilage was depleted of glycosaminoglycans.<sup>57</sup> In other words, there is a greater inhibition of PRG synthesis in osteoarthritic cartilage than normal cartilage. Other researchers have confirmed these findings that NSAIDs consistently suppress proteoglycan and glycosaminoglycan synthesis.<sup>58-60</sup> This depletion of matrix proteoglycans has been shown to be one cause of the increased degeneration of cartilage chondrocytes from the use of NSAIDs.<sup>61</sup> Taken to the extreme, one researcher put it this way, "...depending on dose and at concentrations that in many cases correspond to therapeutic plasma levels, these drugs may lead to a pronounced reduction or complete blockade of synthesis of the proteoglycans and collagen of the cartilage matrix." They went on

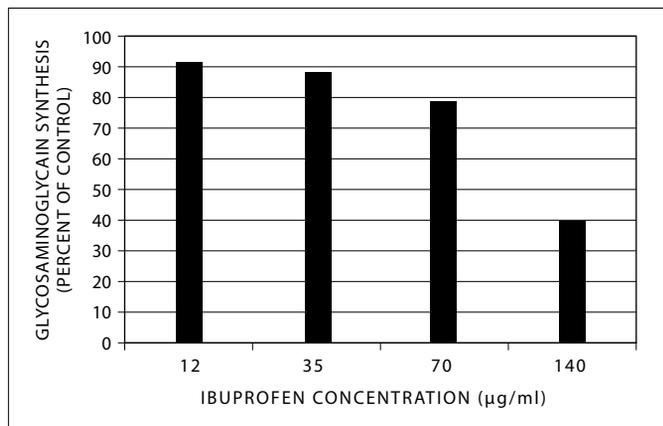
**P-value** is the sense of statistical significance.  $P < 0.01$  means that there is a less than 1 in 100 (1%) chance that the results occurred by chance. The lower the p-value, the more significant the result.

to say that the medications can "induce progressive joint degeneration within three to four months."<sup>62</sup> Animal studies have also shown the effects of NSAIDs on proliferation, cell cycle kinetics, cytotoxicity, and cell death of chondrocytes. In one study the NSAIDs indomethacin, ketorolac, diclofenac, piroxicam, and celecoxib inhibited thymidine incorporation of chondrocytes at therapeutic concentrations. NSAIDs also arrested chondrocytes in their cell cycles, thus inhibiting chondrocyte cell replication. Upon 24 hour exposure to indomethacin, ketorolac, diclofenac, and piroxicam, chondrocyte cell death (both apoptosis and necrosis) was induced in cell cultures.<sup>63</sup> One mechanism by which NSAIDs are toxic to chondrocytes is by inhibiting PGE<sub>2</sub> synthesis by chondrocytes.<sup>64</sup> PGE<sub>2</sub> elicits differentiation of chondrocytes and is an important contributor to cartilage formation and promotes DNA and matrix synthesis in chondrocytes.<sup>65, 66</sup> PGE<sub>2</sub> has a growth stimulatory effect on chondrocytes, thereby increasing chondrocyte DNA synthesis.<sup>67, 68</sup> NSAIDs inhibit the enzyme cyclooxygenase which is responsible for PGE<sub>2</sub> release in chondrocytes.<sup>69</sup>

HUMAN STUDIES

In 1991, Kenneth D. Brandt, MD, one of the main researchers on NSAIDs' effect on cartilage wrote, "No clinical evidence exists today, however, to support the contention that NSAIDs favorably influence the progression of joint degeneration in man."<sup>70</sup> While this author will not refute this statement, an addition to it is warranted ...but much evidence exists that NSAID use accelerates articular cartilage degeneration. This issue is extremely important since 30 billion over-the-counter doses of NSAIDs are sold annually in the United States.<sup>71</sup>

While the condition known as osteoarthritis has other names, including degenerative joint disease, the name is actually misleading; the words do not accurately describe the pathophysiology of the condition. The term osteoarthritis literally means inflammation of a bony joint but the most common clinical presentation of the condition is one of articular cartilage breakdown without joint swelling, heat, or any other markers of inflammation. The more appropriate term for osteoarthrosis or degenerative joint disease is understood as a non-inflammatory degenerative process. The notion of treating a non-inflammatory condition with an anti-inflammatory medication is bound to have long-term detrimental effects.

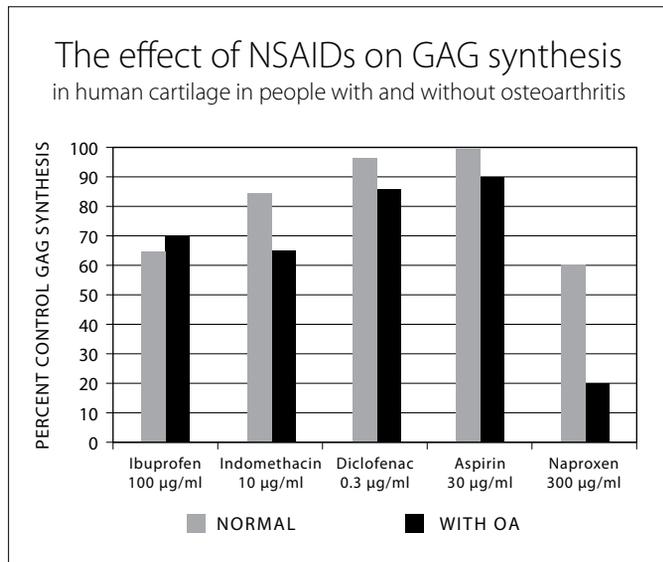


**Figure 10. Net synthesis of <sup>35</sup>S-glycosaminoglycans by normal canine knee cartilage cultured in the presence of ibuprofen.** Ibuprofen inhibited glycosaminoglycan synthesis by cartilage cells at doses that are commonly achieved by those taking this medication.

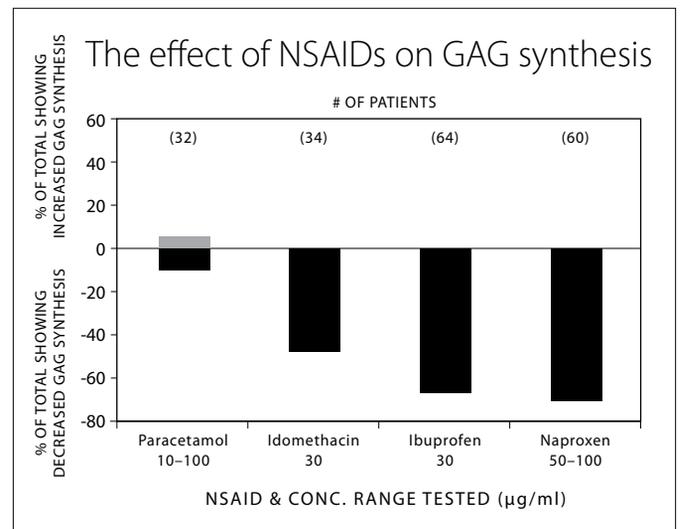
At present no quantitative non-invasive method for determining the anabolic (building up) and catabolic (breaking down) activity of NSAIDs on human cartilage *in vivo* exists. Most information on the effects of NSAIDs on the turnover of extra-cellular matrix macromolecules comes from short-term organ culture studies. Initial evaluations into the pathophysiology of osteoarthritis concentrated on the effects of NSAIDs on glycosaminoglycan synthesis. It was established that in all but the most severe cases of osteoarthritis, the chondrocyte response to proteoglycan depletion was an increase in glycosaminoglycan synthesis.<sup>72, 73</sup> One of the first to show that NSAIDs diminished glycosaminoglycan synthesis in aged human cartilage cells (taken during hip surgery) *in vitro* was a research group from the University of Sydney in 1976.<sup>74</sup> J.T. Dingle, led several of the follow-up studies on the effects of NSAIDs on human cartilage metabolism. The initial studies revealed significant declines in glycosaminoglycan synthesis in both normal and osteoarthritic human cartilages.<sup>75</sup> (See Figure 11.) In a follow-up study, the same research group, took femoral head articular cartilage from non-arthritic and osteoarthritic patients post-operatively after total hip replacement. The relative human cartilage metabolism

*in vivo* – experimentation using whole, living organisms or live isolated cells. Once the cells are disrupted and the individual parts are treated or analyzed this is known as *in vitro*.

was measured on 245 osteoarthritic patients and 80 normal patients' cartilage organ cultures subjected to various NSAIDs. The commonly used NSAIDs indomethacin, ibuprofen, and naproxen were shown to significantly inhibit (from 40 to 70%) glycosaminoglycan synthesis in patients' cartilage.<sup>76</sup> (See Figure 12.) Notice that paracetamol (acetaminophen or Tylenol) did not inhibit GAG synthesis. The researchers noted that caution must be exercised in extrapolation from *in-vitro* (lab) to *in-vivo* (person) effects of NSAIDs, but it seems possible that some highly effective anti-inflammatory agents may produce adverse effects on cartilage integrity when employed during long-term treatment.<sup>77</sup> Other researchers have confirmed NSAIDs' inhibitory effect on proteoglycan synthesis and have commented that "...any drug that suppresses proteoglycan synthesis and impairs the ability of the chondrocyte to repair its damaged extracellular matrix, could potentially accelerate the breakdown of the articular tissue."<sup>78, 79</sup>



**Figure 11. The effect of NSAIDs on GAG synthesis in humans (both non-arthritic and osteoarthritic) is shown.** Concentrations of NSAIDs are similar to those obtained in serum/synovial fluid during treatment.

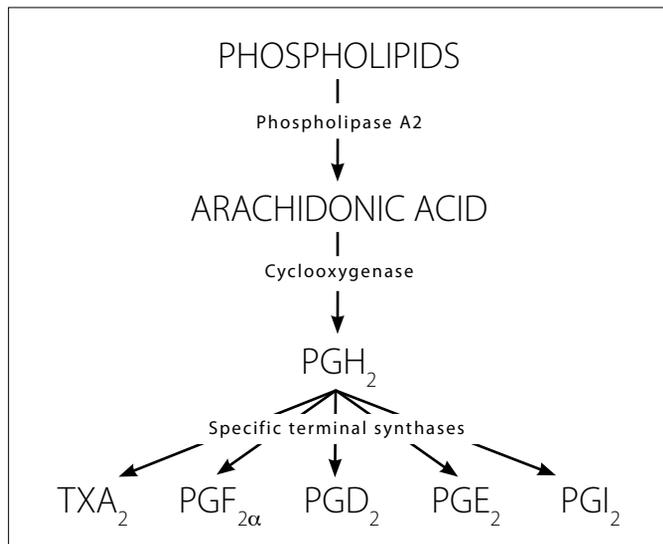


**Figure 12. Some of the most commonly used NSAIDs, Indomethacin, Ibuprofen, & Naxopren, were found to decrease GAG synthesis, whereas Paracetamol (acetaminophen) did not.**

NSAIDS INHIBIT PROSTAGLANDIN SYNTHESIS

One way in which NSAIDs stop the chondrocytes from repairing themselves is by the inhibition of the synthesis of Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). Prostaglandins (PG) are produced by most human cell types (including chondrocytes) and have a variety of physiologic functions. PG synthesis is initiated by the mobilization of arachidonic acid from cell membrane phospholipids as a result of the enzyme phospholipase A<sub>2</sub>. The enzyme

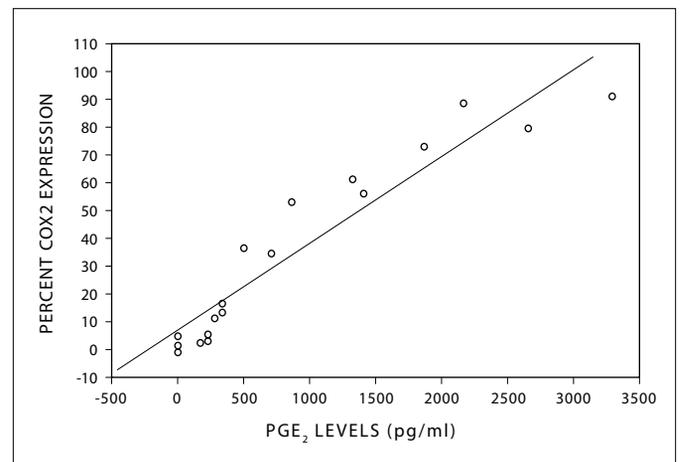
cyclooxygenase along with other enzymes converts arachidonic acid to five primary prostaglandins:  $\text{PGD}_2$ ,  $\text{PGE}_2$ ,  $\text{PGI}_2$  (Prostacyclin),  $\text{PGF}_{2\alpha}$ , and  $\text{TXA}_2$  (thomboxane). (See Figure 13.) These PGs have a variety of functions including the mediation of inflammation, calcium movement, sensitization of spinal neurons to pain, blood clotting, blood pressure, circulation, control of blood flow in kidneys, hormone regulation, protection of gastrointestinal lining, and the control of cell growth.<sup>80, 81</sup> Chondrocytes and synovial fibroblasts produce  $\text{PGE}_2$ .  $\text{PGE}_2$  levels are increased to an impact load on articular cartilage or during cartilage degeneration.<sup>82, 83</sup>  $\text{PGE}_2$  is reported to have anabolic effects on cartilage: increasing proteoglycan and DNA and collagen synthesis,<sup>84, 85</sup> stimulating proliferation and proteoglycan aggrecan synthesis,<sup>86, 87</sup> and, at low concentrations, stimulating type II collagen synthesis.<sup>88</sup>



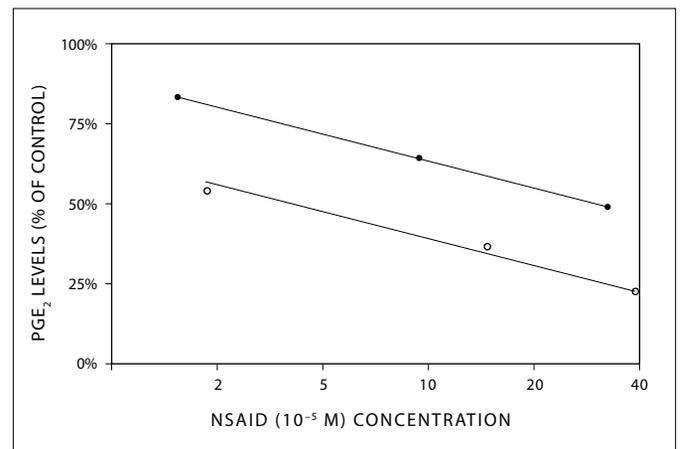
**Figure 13. Biosynthesis of prostaglandins.** The enzyme cyclooxygenase is the key enzyme in the formation of the five primary prostaglandins including  $\text{PGE}_2$ . NSAIDs inhibit prostaglandin synthesis by inhibiting the enzyme cyclooxygenase.

Human chondrocytes express two forms of the cyclooxygenase enzyme, known as the COX-1 and COX-2 isoforms. Unstimulated human chondrocytes do not contain detectable COX-2.<sup>89</sup> COX-1 is present in most cells under physiological conditions, whereas COX-2 is induced by some cytokines presumably in pathological conditions such as joint trauma, degeneration, or osteoarthritis.<sup>90, 91</sup> Put another way, COX-2 is undetectable in most normal tissues, is an inducible enzyme, becoming abundant in activated macrophages (immune cells) and

other cells at sites of inflammation. Prostaglandins, whose synthesis involves COX-1, are responsible for maintenance and protection of the gastrointestinal tract, while prostaglandins, whose synthesis involves COX-2, are responsible for inflammation and pain. One of the main prostaglandins involved in this inflammatory reaction is  $\text{PGE}_2$ . Researchers have shown that the  $\text{PGE}_2$  levels correlate with the amount of COX-2 expression in chondrocytes.<sup>92</sup> (See Figure 14.) Also well established is that this  $\text{PGE}_2$  release can easily be inhibited by the use of NSAIDs.<sup>93, 94</sup> (See Figure 15.) Since the over expression of the COX-2 protein plays an important role in many pathophysiologic states, including inflammation, cancer, angiogenesis, Alzheimer’s disease, and several forms of inflammatory arthritis, NSAIDs especially those that



**Figure 14. Correlation analysis of COX-2 expression and  $\text{PGE}_2$  levels by chondrocytes.** The isoform COX-2 enzyme levels correlate directly with  $\text{PGE}_2$  levels.



**Figure 15.  $\text{PGE}_2$  released into culture medium, as a function of log-NSAID dose (M).** Results are expressed as % of control values. ● — ● ASA; ○ — ○ TA. NSAIDs at physiologic concentrations are potent inhibitors of  $\text{PGE}_2$  synthesis.

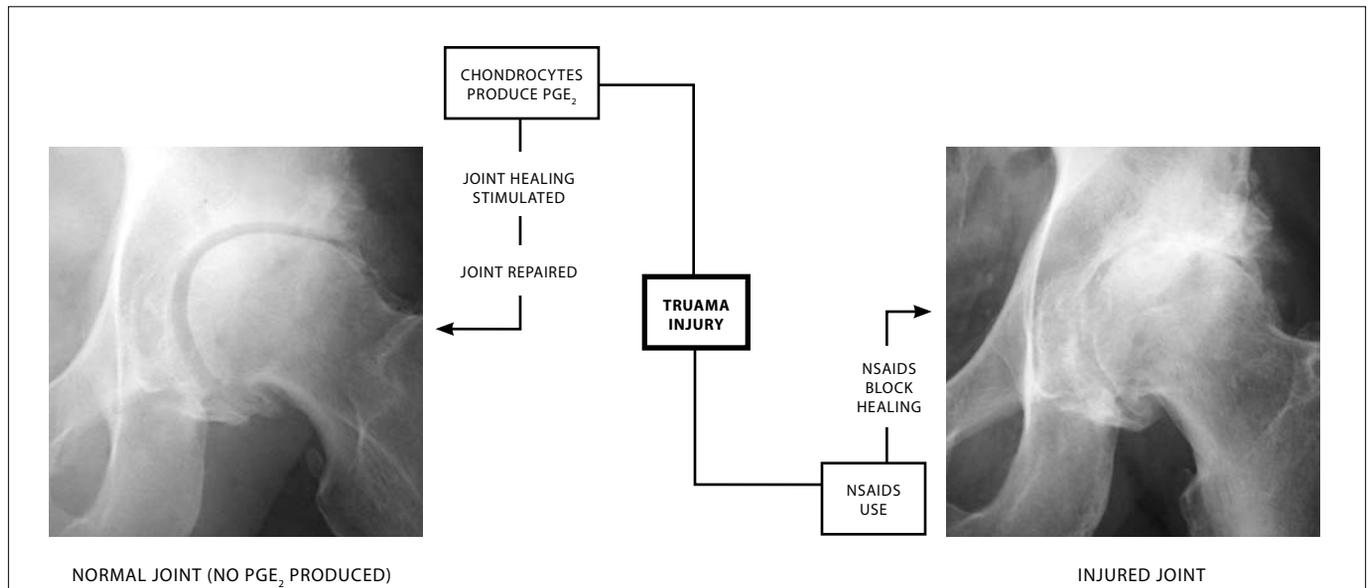
inhibit COX-2, are used for many of these conditions. In regard to joint inflammation, one author notes, "...by inhibiting joint conditions, they (NSAIDs) may indirectly be beneficial to cartilage, specifically when inflammation is primary in the cause of cartilage damage, as in the case for rheumatoid arthritis." However, in OA, in which inflammation may contribute to but is not primarily responsible for cartilage damage, adverse direct effects of NSAIDs on cartilage with long-term treatment may have an important impact on long-term outcome.<sup>94</sup> In other words PGE<sub>2</sub> can exert catabolic or anabolic effects depending on the microenvironment.<sup>95</sup>

Since normal articular chondrocytes produce very little PGE<sub>2</sub> and osteoarthritic chondrocytes produce a lot of it through the COX-2 enzyme, it would make sense from a traditional medical point of view to attack arthritis pain from this angle. This is especially true since the over expression of the COX-2 protein (and thus increased PGE<sub>2</sub> levels) plays an important role in many pathophysiological states, including systemic inflammation, fever, cancer, angiogenesis, Alzheimer's disease, and inflammatory arthritis.<sup>96</sup> Yes, in certain conditions inflammation is harmful, but it is a big leap to assume everywhere there is PGE<sub>2</sub> it is harming tissue. The articular chondrocytes make PGE<sub>2</sub> in response to injury to stimulate healing. Osteoarthritic cartilage spontaneously releases PGE<sub>2</sub> in levels at least 50-fold higher than normal cartilage and

18-fold higher than normal cartilage stimulated with cytokines and endotoxin.<sup>97-100</sup> The inflammation that occurs through PGE<sub>2</sub> when a normal or osteoarthritic joint is injured is the body's immune system response to try and get the joint injury repaired.<sup>101</sup> When a person uses medications that block this response, while pain may be improved, the repair mechanisms for the joint are inhibited. The long-term consequences, of course can be an acceleration of the degenerative osteoarthritic process. (See Figure 16.) Long-term NSAID treatment not only blocks PGE<sub>2</sub> production by direct inhibition of COX-2 activity but by down-regulating COX-2 synthesis.<sup>102</sup>

NSAIDS ACCELERATE THE RADIOGRAPHIC PROGRESSION OF OSTEOARTHRITIS OF THE KNEE AND HIP

The suggestion that indomethacin accelerates the bone destruction in osteoarthritis of the hip was first made by Coke in 1967;<sup>103</sup> subsequent reports have been numerous that provide further clinical evidence of the damaging effects of non-steroidal anti-inflammatory drugs on osteoarthritic hips.<sup>104-107</sup> In one retrospective investigation of the relationship between the use of non-steroidal anti-inflammatory drugs on hip destruction in primary osteoarthritis of the hip, 70 hips were studied in 64 patients. Cranial acetabular migration, a measure of acetabular destruction, was present in 37 hips and absent in 33. Regular intake of NSAIDs was noted for



**Figure 16. Chondrocytes produce PGE<sub>2</sub> in response to injury. NSAIDs, especially those that block COX-2 inhibit PGE<sub>2</sub> synthesis in chondrocytes thereby stalling the body's main inflammatory repair mechanism. Long-term, this will accelerate degenerative osteoarthritis of the joint.**

31 of the 37 migrating hips. In regard to the other six, three took NSAIDs on and off and only three of the 37 did not take NSAIDs. Those patients with serious hip destruction when compared with those who did not have the acetabular destruction did not differ in sex, age, pain grading, or walking ability. The only significant difference was the amount of NSAIDs taken. According to the researchers, NSAID use was associated with progressive formation of multiple small acetabular and femoral subcortical cysts and subchondral bone thinning. They concluded, “The association of acetabular bone destruction with regular NSAID intake in patients with osteoarthritis of the hip adds further evidence to the clinical and experimental observations on the *powerful and potentially harmful effects of these drugs on cartilage and bone.*”<sup>108</sup> In this study the NSAIDs used regularly and associated with acetabular migration in this series were indomethacin (14 hips); ibuprofen (8 hips); naproxen (3 hips); sulindac, aspirin, and piroxicam (2 hips each); flurbiprofen, azapropazone, diclofenac, fenclofenac, and ketoprofen (1 hip each). The authors noted, “This study suggests caution in the widespread use of NSAIDs for osteoarthritis of the hip...”

Researchers in Norway studied the course of osteoarthritis in 294 hips of 186 patients with radiographs over a three year period. The development of the disease in patients treated with an NSAID was compared with that in a control group (no NSAID). In the NSAID group the OA disease progressed at a level of statistical significance more frequently and severely. Specifically the researchers found that in the three year period of the study, the osteoarthritic hips treated with the NSAID had more cysts, altered bone structure, and overall hip destruction. The way they put it was, “In the present study, loss of trabecular structure in the subchondral bone seems to be a characteristic feature in ‘indomethacin joint destruction’ as well as disappearance of normal joint contours and multiple small cysts.”<sup>109</sup> Solomon reported similar destruction in osteoarthritic hip joints as “new events” during treatment with NSAIDs. He performed further investigations on the extirpated (cut out from surgery) femoral heads with examination of cut surface, slab radiographs, and

**By the third year of the study, the results were so dramatic demonstrating the acceleration of the degeneration of the articular cartilage in the knee osteoarthritic patient treated with indomethacin that this part of the study had to be stopped.**

histology. Many of the heads, and especially those with changes attributable to NSAIDs, were found to have microscopic fragmentation of the bony trabeculae giving the appearance of a jammed marrow space.<sup>110</sup> To see if these sort of damaging changes occurred with NSAID use on osteoarthritic knees the Longitudinal Investigation of Nonsteroidal Anti-inflammatory Drugs in Knee Osteoarthritis (LINK) study group was formed in England. They did a large study to compare the rate of radiographic progression in knee osteoarthritis comparing indomethacin (NSAID) with placebo. The study involved 20 rheumatology clinics in the United Kingdom. Patients received indomethacin 25mg three times daily or a placebo. The average person in each group was around 60 years of age and had osteoarthritis in the knee for over five years. The study involved 85 clients in the indomethacin group and 85 in the placebo group. Radiographic analysis was done yearly and the radiographic

grade was judged by two observers using a six point scale. The average length of follow-up was three years. By the third year of the study, the results were so dramatic demonstrating the acceleration of the degeneration of the articular cartilage in the knee osteoarthritic patient treated with indomethacin that this part of the study had to be stopped. There were more than twice as many patients showing deterioration in the indomethacin group as the placebo. The difference between the two groups was highly statistically significant ( $p=0.009$ ). The authors noted that the risk of deterioration within a one year period in patients taking indomethacin relative to placebo was 2.1 (risk ratio).<sup>111</sup> The authors concluded firmly, “Our study confirms beyond a reasonable doubt that indomethacin increases the rate of radiological deterioration of osteoarthritic knees.”

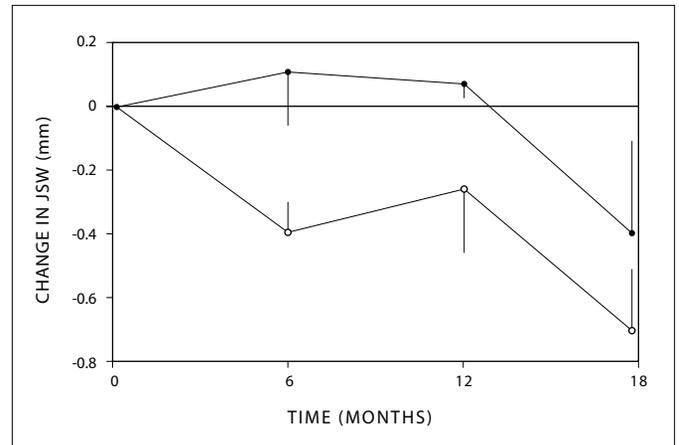
What actually happens to patients who take NSAIDs on a regular basis? If NSAIDs, by inhibiting pain and inflammation in osteoarthritic joints, cause people with OA to overuse a damaged joint, this should result in accelerating joint degeneration and joint replacements at an earlier time or, alternatively, if treatment with NSAIDs alters cartilage metabolism and inhibits joint healing, an acceleration of articular cartilage degeneration should be

seen. Numerous studies have shown that non-steroidal anti-inflammatory drugs, particularly indomethacin, increase the rate of progression of osteoarthritis of the hip and knee.<sup>112-117</sup> Statistically significant progression of hip radiographs in osteoarthritic patients can be seen within one year of those patients taking NSAIDs. In one study, the authors noted, "...a statistically significant correlation between the NSAID consumption score and changes in the radiological parameter ( $p=0.0001$ ). This statistically significant difference was retained when the percentage of days taking NSAIDs was added ( $p = 0.0004$ )."<sup>118</sup>

In a recent landmark study, Dutch researchers studied more than 1600 subjects with hip OA and 635 with knee OA. The researchers evaluated radiographs of the hip and knee at baseline and follow-up. The researchers assessed the associations between different types of NSAIDs and the progression of OA. The mean follow-up period was 6.6 years. They found that long-term use of the NSAID diclofenac was associated with a more than twofold increase in radiologic progression of hip osteoarthritis and a threefold increase in progression observed in the knee. Ibuprofen use was also shown to be associated with a statistically significant increase in progression of the users' knee and hip OA.<sup>119</sup> The interesting point of this study is that the study population was healthy. The authors noted that this may have resulted in an underestimation of the reported associations. Their conclusion noted, "... these data suggest that diclofenac may induce accelerated progression of hip and knee OA. Whether this occurs because of a true deleterious effect on cartilage or because of excessive mechanical loading on a hip or knee following pain relief, remains to be investigated." Another study comparing diclofenac with placebo, as seen in *Figure 17*, accelerated OA in knees as evidenced by a greater decline in joint space width on X-rays compared to placebo.<sup>120</sup>

#### NSAIDS INCREASE THE NEED FOR JOINT REPLACEMENT

It is important to remember that pain has a physiologic function: if a joint produces pain when it is used, it is a signal for the body to use that joint less or else the structure eliciting the pain will be further damaged. One study focused on a group of patients with hip osteoarthritis who needed to have a joint replacement in the not-too-distant future. They were randomly prescribed an NSAID, aspirin-like drug, or acetaminophen. Over the next months, the patients were asked about their joint pain, and radiographs of their hips were taken. The patients given the NSAID



**Figure 17. Graph of the mean (SD) change in joint space width at each 6-month visit in knees with late stage osteoarthritis (joint space width <50% of that in normal healthy knees) in patients receiving either diclofenac (○) or placebo (●).**

Source: Buckland-Wright JC, et al. Quantitative microfocal radiography detects changes in OA knee joint space width in patients in placebo-controlled trial of NSAID therapy. *J Rheumatol.* 1995;22:937-43.

had more progression of their hip radiographs and needed to have joint replacements performed in half the time as the group given acetaminophen. The authors speculated why this occurred. They noted that the NSAID might have prevented normal cartilage turnover and repair, and accelerated the joint degeneration; or, more likely, the potent medication decreased joint pain and those subjects were therefore more active. This has led to the suggestion that potent NSAIDs can lead to "analgesic joint," which can develop when pain is relieved by the NSAID, thus increasing the joint use and subsequent load on the joint, causing accelerated joint degeneration and ultimate need for joint replacement, especially if the excessive joint load continues.<sup>121</sup> This latter notion has actually been studied: patients who take NSAIDs for knee OA put increased joint forces on their knees with walking because of pain relief, compared to those who do not have pain relief taking nothing, or just a placebo. As one researcher put it, "Of particular concern is the fact that anti-inflammatory or analgesic relief may actually be associated with an increase in joint forces."<sup>122, 123</sup> Other researchers have confirmed that the same type of knee joint loads that cause knee osteoarthritis are increased significantly during walking with NSAID use.<sup>124-126</sup> The net effect of increased pressure on the damaged joint would be accelerated osteoarthritis and need for knee or hip replacement. One research team confirmed that NSAID use increases the risk of getting a hip replacement due to primary osteoarthritis by 50% during a two year period.<sup>127</sup> These researchers raised the

question of the deleterious effect on cartilage resulting from NSAID intake in osteoarthritis. Other researchers have also confirmed that NSAID users need total joint replacements sooner than those who do not take them.<sup>128</sup>

OVERALL EFFECTS OF NSAIDS ON OSTEOARTHROTIC JOINTS

It is clear from the scientific literature that NSAIDs from in vitro and in vivo studies in both animals and humans have a significant negative effect on cartilage matrix which causes an acceleration of the deterioration of articular cartilage in osteoarthritic joints. The preponderance of evidence shows that NSAIDs have no beneficial effect on articular cartilage and accelerate the very disease for which they are most used and prescribed. While the rapid deterioration of joints after long-term NSAID treatment can be from a loss of proactive pain sensations, it is much more likely that it is a direct effect of NSAIDs on cartilage. (See Figure 18.) Some of these effects can be seen in Figure 19 and include inhibition of chondrocyte proliferation, synthesis of cellular matrix components, glycosaminoglycan synthesis, collagen synthesis, and proteoglycan synthesis. Clinically this is manifested as an accelerated progression of the knee or hip osteoarthritis as seen by standard radiographs. The long-term consequence of the deterioration of the joint is a need for joint replacement. This author notes that massive NSAID use in osteoarthritic patients since their introduction over the past forty years is one of the main causes of the rapid rise in the need for hip and knee replacements both now and in the near future.



**Figure 18. Effects of NSAIDs on articular cartilage.** A typical X-ray showing cartilage deterioration. Studies have shown that taking NSAIDs not only accelerates this process, but makes it more likely the person will need a joint replacement.

The effect of NSAIDs on joints

- Acceleration of radiographic progression of osteoarthritis
- Decreased joint space width
- Increased joint forces/loads
- Increased risk of joint replacement
- Inhibition of chondrocyte proliferation
- Inhibition of collagen synthesis
- Inhibition of glycosaminoglycan synthesis
- Inhibition of prostaglandin synthesis
- Inhibition of proteoglycan synthesis
- Inhibition of synthesis of cellular matrix components

**Figure 19. NSAIDs taken long term have a negative effect on joint physiology and ultimately lead to degenerative arthritis.**

RECOMMENDATIONS ON THE USE OF NSAIDS IN OSTEOARTHRITIS

The preponderance of scientific evidence shows that NSAIDs damage articular cartilage. Various scientific papers and consensus groups have stated that there is no convincing data to show that the widely used NSAIDs and recommended selective COX-2 inhibitors have favorable effects on cartilage.<sup>129-131</sup> Even the main consensus paper from the International Cartilage Repair Society and Osteoarthritis Research Society International stated that NSAID use has to be limited to the short term. Specifically the recommendation was as follows: In patients with symptomatic hip or knee osteoarthritis, non-steroidal anti-inflammatory drugs (NSAIDs) should be used at the lowest effective dose but their long-term use should be avoided if possible.<sup>132</sup> They also noted that NSAIDs should not be first-line therapy for joint OA. Other groups have raised similar sentiments. The committees of the International League Against Rheumatism and the World Health Organization came up with guidelines for the testing of new drugs in osteoarthritis. The consensus from these meetings resulted in recommendations by The European Group for the Respect of Ethics and Excellence in Science (GREES) for governmental registration and approval of new drugs used in the treatment of OA and have added the requirement that the drug not have a deleterious effect on the diseased and non-diseased contralateral joint; i.e., no deleterious effect on osteoarthritic or normal cartilage.<sup>133</sup> If this latter recommendation were followed, the vast majority, if not all NSAIDs, would be immediately taken off the market and no new ones would get approved.

While it is admirable for the various consensus and rheumatology organizations to educate doctors and the lay public about the necessity to limit NSAID use in OA, this author (RH) feels the warnings are not enough. Within the last year, for instance, the FDA has again implemented new rules requiring stronger and more extensive label warnings (in addition to the heart disease risks) regarding the risk of liver damage and stomach bleeding for people taking common over-the-counter pain relievers. As for NSAIDs, the new regulations require front labels to instruct users to see new warnings that say, “This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause severe stomach bleeding. The chance is higher if you are age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinning or steroid drug, take other drugs containing prescription or nonprescription NSAIDs, have three or more alcoholic drinks every day using this product, take more or for a longer time than directed.”<sup>134</sup>

The lay public for whom NSAIDs are prescribed and recommended by both health care professionals and drug manufacturers should be aware that long-term NSAID use is detrimental to articular cartilage. Specifically, be informed that NSAIDs will likely worsen the OA disease for which it is prescribed. Physicians, allied health care professionals, and drug manufacturers should be required to inform the lay public that NSAID use can accelerate OA articular cartilage degeneration. A strict warning label on these medications should read as follows:

*The use of this nonsteroidal anti-inflammatory medication has been shown in scientific studies to accelerate the articular cartilage breakdown in osteoarthritis. Use of this product poses a significant risk in accelerating osteoarthritis joint breakdown. Anyone using this product for the the pain of osteoarthritis should be under a doctor’s care and use of this product should be with the very lowest dose and for the shortest possible duration of time.*

One of the basic tenants of medicine is stated in the Hippocratic oath, “I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone.”<sup>135</sup> For doctors to uphold this statement in the treatment of their OA patients, it would necessitate the almost complete banning of the use of NSAIDs for this condition. If this does not occur, then most likely the exponential rise in degenerative arthritis and subsequent musculoskeletal surgeries, including knee and hip replacements, as well as spine surgeries, will continue for decades to come. ■

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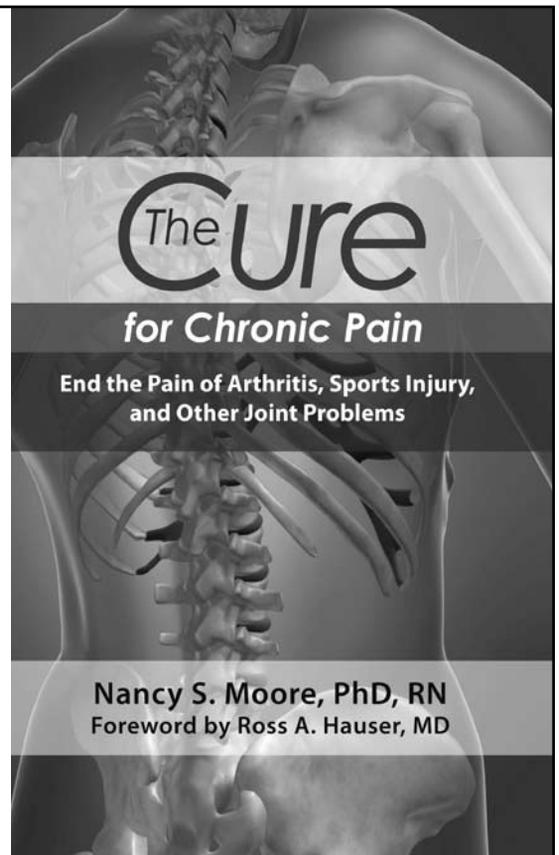
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