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OSTEOARTHRITIS – A NATURAL APPROACH

Arthritis refers to nearly 100 different rheumatic diseases of the areas in and around the joints. Conditions as different as fibromyalgia, scleroderma and gout have often been included with the classic arthritic conditions: osteoarthritis and rheumatoid arthritis. Arthritis is now our nation's leading cause of disability and is projected by the CDC to effect nearly 60 million Americans (20% of U.S. population) by the year 2020. By far the most prevalent type is osteoarthritis, accounting for one half of the 40 million Americans currently suffering from these conditions. Osteoarthritis (OA), often called degenerative joint disease (DJD), is characterized by the degeneration of the cartilage protecting the ends of bones at the joints. We will discuss the underlying problems associated with osteoarthritic joints as well as review the pharmacologic and non-pharmacologic approaches to treat degenerative joint conditions.

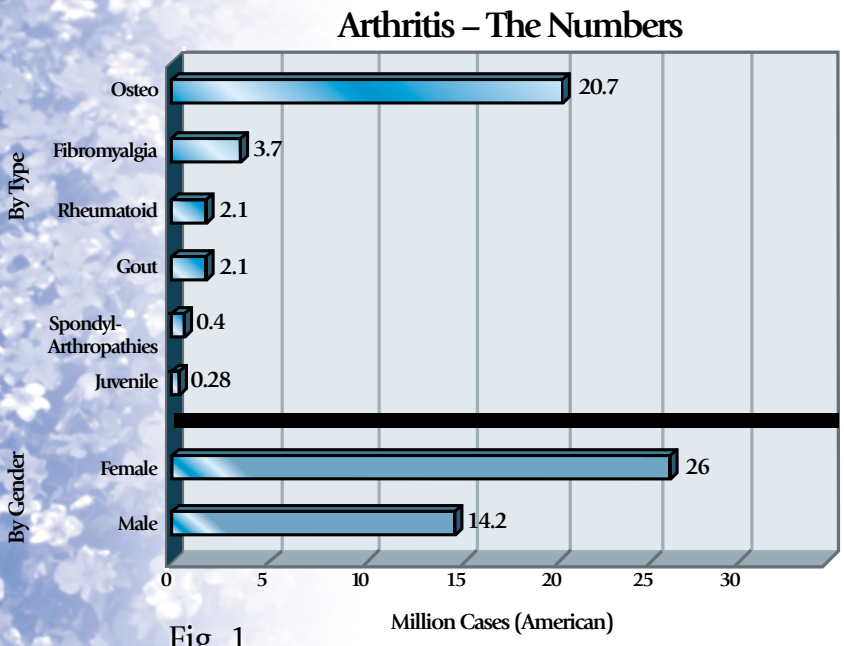

Fig. 1

Osteoarthritis- A degenerative process:

The term arthritis implies an inflammatory process; which in fact may not necessarily be involved in many of the cases of osteoarthritis. It is for this reason that many use the term arthrosis or degenerative joint disease (DJD) for this condition. Unlike rheumatoid arthritis, which usually effects the respective joints symmetrically (both knees, both hands etc.), OA often occurs in one joint without similar pathology in its symmetrical equivalent. Osteoarthritis (OA) is characterized by a slow and gradual onset, usually starting with morning stiffness in a few weight-bearing joints (especially the knees). Eventually, pain is associated with movement leading to loss of joint function. Signs include joint tenderness, intermittent inflammation, joint crepitus and Heberden's nodes (when fingers are involved). X-ray analysis will often show a narrowing in the joint space and irregular (osteophytes) and increasingly dense bone surface. These findings are the result of the wearing away of the articular cartilage covering the ends of the bones at the joint and the irregular compensation of the bone ends. While not considered inevitable, OA is certainly related to the effects

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(continued from page 1)

of time and gravity (bats and sloths are the only mammals with no history of OA) and is often called wear and tear arthritis.

In order to protect the integrity of the bones meeting at synovial joints, the ends are covered by articular cartilage. This cartilage is made of collagen fibers, giving it tensile strength, and proteoglycan molecules (especially chondroitin sulfate), to cushion impacting pressure. The proteoglycan molecules are made from a linear core protein with several hundred molecules of glycosaminoglycans (GAGs, primarily chondroitin sulfate and keratin sulfate) attached at right angles (See Figure 2). These protein core molecules are attached to a hyaluronic acid framework, which acts in a network to make up the articular cartilage. This unique structure allows proteoglycan molecules to absorb synovial fluid when uncompressed and then expel the fluid as it is compressed. This compression and decompression of the proteoglycans allows for the exchange of fluids and nutrients in the joints, where a direct blood supply is not available. Active exercise leads to the compression and decompression of the articular cartilage and is beneficial in preventing OA, as inactivity will lead to nutrient and fluid deprivation of the articular cartilage, hastening its degeneration. Properly hydrated articular cartilage is one of the most frictionless surfaces known.

Cells known as chondrocytes are responsible for forming articular cartilage. Like CNS and muscle cells, chondrocytes have an extremely long cell cycle and do not divide very often. It actually may be the triggering of the chondrocytes to divide, and a coordinated osteoblast bone synthesis that may be responsible for many of the hardening and irregularly formed bone ends. Under normal circumstances, chondrocytes produce proteoglycans by polymerization of the monomers derived from glucose (glucuronic acid and N-acetyl glucosamine) and galactose (See figure 2). Modification of enzymes in these pathways, reduced levels of precursors, or preventing those precursors from entering the chondrocyte (sedentary lifestyle) will decrease the formation of articular cartilage and increase the incidence of OA.

Treatment:

Most consider OA to be an irreversible degenerative process and treatment is primarily to reduce disability and pain. Joint replacement is considered when all therapies fail to reduce pain or increase mobility. Injections of synovial fluid-like liquids into the joint may delay the need for joint replacement. These injections, called viscosupplementation, are done with naturally derived hyaluronic acid (Hyalgan) or synthetic lubricants like Synvisc. Years, and often decades, of pain reduction delays the need for surgical intervention. For this, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS, ibuprofen, naproxen, ketoprofen etc.) and assorted analgesics like acetaminophen are most widely used. The two main concerns with these products are the toxic side effects generated by these products (liver, kidney, gastrointestinal) and their effects on cartilage metabolism.

The toxic side effects of pharmacologic analgesics and anti-inflammatory agents are well known and will only be touched upon. NSAIDS work by inhibiting the enzyme cyclooxegenase-2 (COX-2), blocking the formation of inflammatory prostaglandins. Unfortunately, NSAIDS inhibit the enzyme cyclooxegenase-1 (COX-1) as well, leading to most of the noted side effects. NSAIDS disrupt the gastrointestinal mucosal-protective and acid limiting properties of prostaglandins, leading to gastrointestinal ulceration or even hemorrhages (1). Gastrointestinal complications are the most common reported adverse drug reaction with NSAID use and patients suffering from arthritis the most frequent users of NSAIDS. This has lead to studies of the benefit of concomitant prescription of H-2 blockers, prostaglandin analogs or antacids (2,3). Inhibition of prostaglandins responsible for vasodilation, which oppose the vasoconstricting actions of thromboxanes and leukotrienes upset the balance that maintains renal function, the other major side effects of NSAID use (4). The elderly, who are more likely to be on chronic NSAIDS use for arthritis, may be particularly prone to renal dysfunction. A recent study from the University of Massachusetts Medical School showed that elderly individuals (>70) were nearly twice as likely to have increased levels of laboratory markers of renal dysfunction (BUN, serum creatine, and BUN:serum creatine ratio) when taking NSAIDS (5). The development of COX-2 specific NSAIDS may reduce some of these unwanted side effects, although non-prostaglandin related side effects are also associated with NSAID use.

Acetaminophen (Tylenol®) toxicity is a concern for the liver as well as the kidney, where the P450 enzymes metabolize acetaminophen's highly reactive metabolites (6). Large and repeated doses have been shown to produce hepatotoxicity (7), yet acetaminophen is still the most widely used and

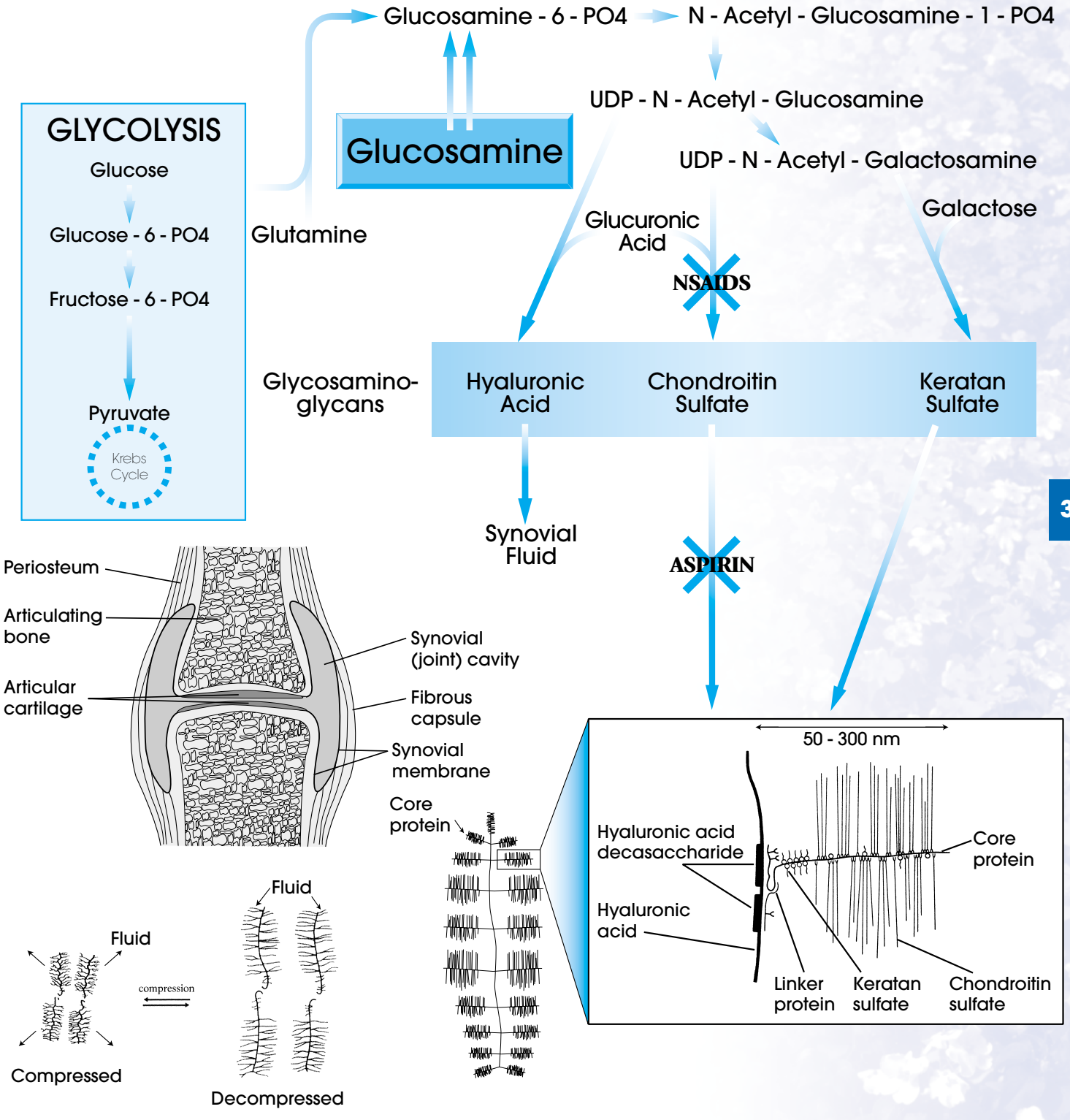
GLYCOLYSIS
Glucose
Glucose - 6 - PO4
Fructose - 6 - PO4
Pyruvate
Krebs Cycle
Glutamine
Glucosamine - 6 - PO4
N - Acetyl - Glucosamine - 1 - PO4
Glucosamine
UDP - N - Acetyl - Glucosamine
UDP - N - Acetyl - Galactosamine
Glucuronic Acid
Galactose
NSAIDS
Glycosamino-glycans
Hyaluronic Acid
Chondroitin Sulfate
Keratan Sulfate
Synovial Fluid
ASPIRIN
Periosteum
Articulating bone
Articular cartilage
Synovial (joint) cavity
Fibrous capsule
Synovial membrane
Core protein
50 - 300 nm
Hyaluronic acid decasaccharide
Hyaluronic acid
Core protein
Linker protein
Keratan sulfate
Chondroitin sulfate
Fluid
compression
Compressed
Fluid
Decompressed

Fig. 2

(continued from page 2)

recommended nonprescription analgesic in the United States.

One of the interesting findings of the use of aspirin, NSAIDS, and steroid drugs for osteoarthritis is their effect on articular cartilage metabolism. NSAIDS, in particular, have been shown to suppress proteoglycan synthesis by chondrocytes (8). To date, contradictory findings show that some NSAIDS block proteoglycan synthesis at certain concentrations while seeming to stimulate synthesis at other concentrations (9,10). Aspirin has been shown to block an enzyme involved in elongation of chondroitin sulfate molecules (11). It seems that the very drugs used to mask the pain caused by articular cartilage loss, may be preventing the joints from effectively replacing it. More studies need to be done to discover the exact relationship of aspirin, NSAIDS, and cortisone use with cartilage metabolism. Until then, it would be prudent to consider alternatives which have been shown to be equally effective, have fewer side effects, and may actually work by helping the joint replace the cartilage and fluid it desperately needs.

Glucosamine:

Glucosamine metabolites are vital for the production of cartilage GAGs such as hyaluronic acid, chondroitin sulfate, and keratin sulfate. While the body can derive Glucosamine-6-phosphate from fructose-6-phospate using the enzyme Glutamine Fructose-6-phosphate amino transferase, it also has the enzymatic machinery to convert preformed glucosamine to glucosamine-6-phosphate and N-acetyl-D-Glucosamine (Fig 2). Research into the ability of exogenous glucosamine to stimulate chondrocyte GAG synthesis has been ongoing for more than 50 years. One of the measures of chondroitin sulfate synthesis, the incorporation of radiolabeled sulfur, is stimulated by the addition of glucosamine and galactosamine (12). Studies published in the 1970s confirmed these reports and found that N-Acetyl-Glucosamine was able to stimulate *in vitro* chondroitin sulfate synthesis, although to a lesser extent than glucosamine salts (13,14,15). It seemed logical to look into glucosamine as a therapeutic agent for osteoarthritis, a disease characterized by cartilage destruction. Pharmacokinetic studies in animals and man have confirmed that glucosamine salts are absorbed at greater than 90% when taken orally (16,17,18).

The early 80's brought a number of clinical studies looking into oral glucosamine treatment for osteoarthritis (20-26). One multicenter study found that of 1208 patients receiving 1.5g of glucosamine per day for 50 days, the treatment was rated "good" or "sufficient" in 95% of the patients (21). Two smaller double-blind, placebo-controlled studies found similar results (23, 26). When compared with ibuprofen, glucosamine was consistently slower at relieving pain, requiring up to 8 weeks to be comparable to ibuprofen (20). After 8 weeks though, glucosamine was rated better, with fewer side effects. Interestingly, the effects of glucosamine continued several weeks after discontinuation, something not seen with NSAIDS. This implies that the glucosamine may in fact be contributing to increased levels of hyaluronic acid and the articular cartilage precursors (19,27). Recent studies have confirmed these results (28,29). Several review articles have been published and have also confirmed these results, calling for continued research into the use of glucosamine (30-33). One recurring theme is the call for a standard set of criterion (pain scores, diary, concomitant NSAID use, range of motion examinations, X-rays) in order to evaluate the effectiveness of these types of products. Glucosamine is commercially available (most often derived from the chitinous shells of sea invertebrates) in stabilized salt forms (HCl and Sulfate), as N-acetyl glucosamine, and in various grades from crude to pharmaceutical. See side bar "Glucosamine Forms" for information on the controversy surrounding the preferred form arguments.

Chondroitin sulfate:

As the major glycosaminoglycan associated with articular cartilage, chondroitin sulfate is uniquely designed to draw water into the joint tissues and hydrate them. This gives it the ability to be compressed when pressure is put on the joint (squeezing out the water) and then rehydrate when the pressure is released. It is primarily because chondroitin sulfate is regularly sulfated (at the 4 or 6 position) that it has this property. The use of purified chondroitin sulfate (derived from bovine or porcine trachea or sometimes shark cartilage) has been used clinically since the late 1980s and into the 1990s for pain associated with osteoarthritis.

Since the size of the chondroitin sulfate molecules are much larger than glucosamine (MW of 4000-50,000 daltons depending on how the material is processed) absorption and pharmacokinetics is a concern. Several studies have shown that in man and animals 70% of radioactively tagged chondroitin sulfate is absorbed (34,35). While most of this is excreted in the urine, the tissue affinity was primarily to the

(continued from page 4)

synovial fluid and cartilage (34-36).

Both double-blind, placebo-controlled studies as well as open studies showed a consistent benefit, decreasing the need for NSAID use, in patients with osteoarthritis (37,38). One of the hallmark studies was done in Italy and published in 1996 (39). 146 patients with knee osteoarthritis were recruited and randomly placed into one of two groups; one group receiving 50 mg of an NSAID (diclofenac sodium) three times per day or sachets containing 400 mg of chondroitin sulfate three times per day. The study included placebos for both the NSAID and chondroitin sulfate. Treatments ended after three months, although both groups received placebo sachets for another 3 months (6 months total). The authors found that while the NSAID gave predictably quick results, the pain reappeared after active treatment was ended. Chondroitin sulfate, on the other hand, required more time to see a therapeutic response but lasted at least 3 months after active treatment was discontinued.

Most of the recent research in the use of chondroitin sulfate for osteoarthritis was presented in conjunction with the OARS Congress on June 8, 1997 in Singapore (papers published as Supplement A of the May 1998 issue of Osteoarthritis and Cartilage) and the XIth EULAR Symposium in Geneva in 1998 (Published as Litera Rheumatologica 24). Both symposia were sponsored by IBSA, a manufacturer of Chondroitin sulfate in Switzerland. These studies confirmed the use of chondroitin sulfate in knee osteoarthritis (40,41), as well as finger joint OA (42). Additionally they showed that a single dose of 1200mg is therapeutically equivalent to 400 mg in three divided doses per day (43). Further studies showed that while 1200 mg per day initially (first 2 weeks) had better results than 800 mg per day; these differences were no longer evident after 6 weeks (44). This amount (800 mg/d) was then used in a one year randomized double-blinded clinical trial versus placebo. After 1 year of treatment, the functional impairment in all clinical criteria was reduced by 50% and was tolerated by more than 90% of patients (45). The authors concluded that although chondroitin sulfate has been considered a symptomatic slow-acting drug for OA (SYSADOA, a title that glucosamine can also claim) for some time, X-ray analysis revealing improvements of interarticular space have led them to suggest chondroitin sulfate may act as a structure/disease-modifying anti-OA drug (S/DMOAD, a claim postulated for glucosamine). Demonstrated mechanisms thought to contribute to the activities of chondroitin sulfate include 1) anti-inflammatory activity with an affinity to synovial cartilage; 2) metabolic effects on synthesis of hyaluronate and cartilage proteoglycans; 3) inhibition of cartilage degrading enzymes (collagenase, elastase, proteoglycanase) (46). The combination of chondroitin sulfate (800-1200mg per day) with glucosamine (1500 mg /day) has the potential to be a very effective treatment for osteoarthritis, a conclusion which has been reviewed and tested (47,48). A sixteen week trial using glucosamine HCL (1500 mg/day) and chondroitin sulfate (1200 mg/day) with 228 mg of manganese ascorbate was used in a double-blind, placebo-controlled, cross over trial with placebo in 34 males with chronic pain and radiographic degenerated joint disease in the knee and low back (U.S. Navy diving and special warfare communities) (49). The results were statistically significant for the knee in 4 months, although the results for the spine were inconclusive. They conclude that a larger study needs to be conducted to determine whether there is a combined (additional or synergistic) benefit to include both glucosamine and chondroitin sulfate in the treatment of OA.

Sulfur/Methionine containing molecules:

The importance of sulfur, in the form of sulfate, is very important to the integrity and function of articular cartilage. The polyanionic structure that is created by sulfating every other monomer along the chondroitin sulfate chain is one of the factors that make it able to act as a cushion and lubricating surface. A recent study from Italy has shown that arthritic cartilage in horses has only one-third as much sulfur as normal equine cartilage (50). The use of sulfur/methionine containing molecules has been centered around three molecules; S-adenosylmethionine (SAMe), Dimethylsulfoxide (DMSO), and Methylsulfonylmethane (MSM, sometimes called Dimethylsulfone $DMSO_2$). We will briefly review the literature and theories concerning the use of these molecules for osteoarthritis.

Of these molecules, SAMe has had the most published literature, although very little has been published since the data presented at a symposium in May of 1986 in New York titled "Osteoarthritis: the clinical picture, pathogenesis, and management with studies on a new therapeutic agent, S-adenosylmethionine" (published in the November issue of American Journal of Medicine). One of these

Glucosamine Forms:

The debate over which form of glucosamine; hydrocloride (HCl), sulfate (SO4), or N-acetyl-glucosamine (NAG), has been waged to the confusion of both doctor and patient alike. A brief history and rational approach may prove these debates to be fruitless.

The initial in vitro studies using glucosamine used the HCl form (12). These showed an increase in the rate of sulfur incorporation into chondroitin sulfate. In 1971 Karzel and Domenjoz (13) compared glucosamine HCl, glucosamine HI, glucosamine sulfate, glucosamine base, N-acetyl glucosamine, galactosamine, N-acetyl-galactosamine and glucuronic acid. Their findings were that glucosamine salt derivatives (HCl, HI, sulfate) were slightly better at increasing GAG synthesis than the glucosamine base. NAG had a positive, but lesser benefit. All the others tested were of no significant benefit. They state "glucosamine HCl seems to possess a somewhat stronger effect than the 2 others [salt] compounds. This, however, is only true for a comparison on the basis of absolute concentrations. If the results are calculated with reference to the molecular weights of the compounds no difference between the 3 compounds is demonstrable." This essentially means that since glucosamine HCl has more glucosamine by weight than the sulfate form, it would be expected to also stimulate more cartilage synthesis, which it did in these experiments. This tells us that it is the glucosamine portion effecting cartilage synthesis rather than its stabilizing anion. Furthermore, both of these forms ionize completely in the stomach and absorb to the same extent.

The complication came in the early 1980s when Rotta Research Laboratory (Italy) began exclusively using glucosamine sulfate, for which they had a patent, in clinical trials. Interestingly, in 1978 a group from Rotta had published a study proving the effects of glucosamine HCl on both GAG synthesis and cartilage protein synthesis (15). It would seem the choice to use the sulfate form was a wise marketing decision, as the HCl form was not protected by a patent. In the decade following, Rotta was directly involved or supported dozens of studies on the oral use of glucosamine sulfate for osteoarthritis. Not surprisingly, these studies proved that glucosamine was very beneficial for this condition (see main article). This unfortunately led many to believe (and repeat) that the sulfate form was preferable. It certainly had more clinical data, but this was essentially because the sulfate form was the only form used in the trials. The confusion was furthered by the pharmacokinetic study (17) published in 1993 by Setnikar et al (Rotta Research). The study claims to follow the absorption and dissemination of radiolabeled glucosamine sulfate. A careful analysis of the paper shows that "Uniformly labelled 14C-D-glucosamine was obtained from Amersham International Limited with a specific radioactivity of 1.23 mCi/mg. The product was supplied as hydrochloride in a 0.615% aqueous solution. The solution was diluted with unlabelled GS [glucosamine sulfate] and water to obtain the final preparation with the desired radioactivity." Their conclusions should have been for glucosamine in general, and not the particular sulfate form.

If there is a preferred form, it would simply be a salt form (HCl or sulfate). These seem to work better than the NAG form, which has reduced in vitro activity and is considered to be much less absorbable (although this is still under investigation (66)). Finding reliable, pharmaceutical grade glucosamine salts from a source you trust, is by far the most preferable form. Those who would continue this argument are still more concerned about form than substance.

(continued from page 5)

articles reviewed clinical studies that collectively included about 22,000 patients over 5 years that support clinical effectiveness and tolerability (51). Several other studies compared SAMe (1200 mg/d) with NSAID treatment and found that it was equal in clinical effectiveness (pain, morning stiffness, active and passive mobility) with fewer side effects than NSAIDs for hip and knee osteoarthritis (52-55). Long-term studies found similar results using 400 mg/d (56). An additional benefit with SAMe may be it's antidepressive activity, the more current interest of SAMe use, a condition that is often associated with chronic pain. The proposed mechanisms include improving proteoglycan metabolism (57) and direct anti-inflammatory activity (58).

DMSO gained popularity in the early 1980's primarily as a topical analgesic. DMSO gel (25%) was able to have a clinically relevant analgesic effect, when compared to placebo, for patients with osteoarthritis

(continued from page 6)

(61). Its analgesic effect may be due to its ability to block conduction along C-type nerve fibers, responsible for conduction of chronic pain (59) (something also attributed to capsaicin (60)). When DMSO was approved for use in patients with interstitial cystitis, researchers began looking at the similar molecule $DMSO_2$ (more popularly called MSM, methylsulfonylmethane). Very little has been published on the research of using MSM for osteoarthritis. Many of the benefits that have been attributed to MSM, comes from extrapolations of the DMSO research. Most of what is popularly known about MSM has been published in a book called "The Miracle of MSM" (62). The authors, Jacob and Lawrence, have been using DMSO and MSM for several decades and speak highly of its use for all sorts of chronic pain and inflammatory conditions. It seems that the mechanisms sighted for DMSO and MSM would make them more suitable for chronic inflammation (such as rheumatoid arthritis) than degenerative joint disease. One published study (unfortunately in Russian) showed that mice given DMSO or MSM orally had fewer "destructive changes in the joint" (63). While oral MSM therapy (2-8 g/d) may turn out to be an excellent adjunct to glucosamine and chondroitin sulfate for osteoarthritis, the current literature has yet to confirm the excellent reports from various clinical sources.

Vitamin and Mineral:

There is only limited research associated with vitamin or mineral deficiencies and the incidence or pathology of degenerative joint disease. Both Vitamin E and C have been used therapeutically for osteoarthritis, presumably by enhancing articular cartilage stability (64). The enzymes that make cartilage have need of vitamin A, E, pyridoxine, zinc, manganese and copper; a multivitamin that provides the full complex of vitamins and minerals would benefit patients with osteoarthritis. A recent study induced a cartilage matrix deficiency by limiting vitamin B6 in birds (67). Additionally, manganese in particular, when deficient, has been associated with decreased glycosaminoglycan synthesis (65,66). Although this relationship has not been confirmed in humans, several manufacturers add manganese to glucosamine/chondroitin sulfate products for this reason.

Botanical Ingredients:

There are many herbs or herbal extracts that have been used for arthritis, although to date most of these are used for their anti-inflammatory activity such as turmeric (*Curcuma longa* L.), *Boswellia serrata*, or bromelain (from pineapple stems); or analgesic activity such as capsaicin (*Capsicum annuum* L.), or willow bark (*Salix alba* L.). The higher incidence of osteoarthritis in women has led to phytoestrogenic treatments in women with herbs such as alfalfa (*Medicago sativa* L.), and licorice root (*Glycyrriza glabra* L.). Since these treatments are secondary to the joint degeneration we will not discuss them in this review, although judicious use of these botanicals may help resolve many of the symptoms associated with osteoarthritis, as well as other rheumatic conditions.

Conclusion:

Since the publishing of "The Arthritis Cure" by Jason Theodosakis et al in 1997, the medical community and the public have been talking about alternative treatments for osteoarthritis. The unique physiology of the articular cartilage coupled with the chronic nature of this degenerative process makes this condition ideally suited for a non-pharmacologic approach. Add to this, the paucity of beneficial pharmacologic therapies and the increased likelihood of possible damage to cartilage metabolism posed by such therapies, and the use of glucosamine and chondroitin sulfate seems to be more than logical. Furthermore, the biochemical pathways suggest that by providing these two compounds we may actually be halting or reversing these degenerative processes; ultimately delaying or preventing the need for permanent surgical intervention.

The approach then is quite clear: Make sure the patient's complaints are indeed caused by a degenerative process in the joint, eliminate those things exacerbating the condition (obesity, sedentary lifestyle, repetitive motion stress), address hormonal conditions (if applicable), insure the patients is sufficiently complemented with vitamins and minerals, address secondary inflammatory conditions (several botanicals are excellent for this) and finally begin a regimen including glucosamine and/or chondroitin sulfate. Those patients with patience will find that this may be the treatment they have been waiting for.

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