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DRUG TOPICS

The Role of Glucosamine and Chondroitin Sulfate

in the

Management of Arthritis



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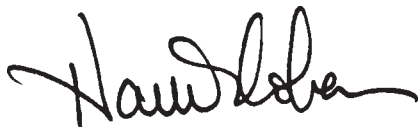
Dear Colleague:

That stiff and aching back... the bum knee that goes out when you hurry down the steps.. the relentless crick in the neck. In a greying population, these and other common symptoms of osteoarthritis will become more and more prevalent and take an increasingly higher toll both financially and on life quality.

Fortunately, new research has begun to yield more innovative approaches to this age-old malady. Here, groundbreaking treatment avenues are addressed in "The Role of Glucosamine and Chondroitin Sulfate in the Management of Arthritis," by W. Marvin Davis, Ph.D., Professor, Department of Pharmacology; Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi. Focusing on restoration of joint cartilage, the author begins by explaining cartilage's function and composition, then goes on to cover the new "matrix enhancement" method of rebuilding this crucial tissue. To round out the discussion, he also addresses more conventional means of handling osteoarthritis, including pain management and corticosteroid therapy.

We are pleased to be able to offer this outstanding continuing education presentation to the pharmaceutical community. We look forward to providing you with this valuable educational material.

Sincerely,



Harold E. Cohen, R.Ph.
Publisher
Drug Topics

The Role of Glucosamine and Chondroitin Sulfate in the Management of Arthritis

by W. Marvin Davis, Ph.D., Professor, Department of Pharmacology; Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi

Introduction

Joint disorders are among the most frequently reported causes of physical impairment in the adult population of the United States. According to the Arthritis Foundation, An estimated 40 million Americans are currently afflicted with joint problems. It is estimated that by the year 2020, 60 million people will have the disease. A variety of therapies are available to reduce their symptoms. Pharmacists can play a unique role in counseling patients on selection and use of appropriate therapies. To this end, a good basic knowledge of joint structure and function is necessary for such counselling to be conducted with appropriate understanding.

The purpose of this article is to provide an overview of joint disorders and their management. This will begin by reviewing the structure of joints and emphasizing the important role of cartilage in both normal and abnormal joint physiology, and then describing cartilage disorders and available therapies

Macroscopic Anatomy: Structure of a Synovial Joint^{1,2}

A joint is any junction of two or more bones. Movable joints, known as synovial joints, are structured to allow smooth, controlled movement while maintaining strength and support. Component parts of a joint include the participating bones composed of dense cortical bone in the shaft, and more spongy trabecular bone in the marrow cavity and at the ends of the bone. Joints are held together by ligaments, which permit movement in certain axes but prevent other movements; the range of motion

possible is characteristic of the given joint. The surfaces of the bones where they make contact with each other are covered with articular cartilage.

Surrounding the small space between the two bones of a joint is the joint capsule, which is composed of a fibrous outer layer and an inner layer of synoviocytes. These are specialized cells that secrete synovial fluid, which lubricates and cushions the joint and also enables nutrients to reach the articular cartilage. Bone is covered by a fibrous membrane called periosteum ("around the bone"), and the membrane surrounding articular cartilage is the perichondrium ("around the cartilage").

Of all these component parts, the articular cartilage plays assuredly the most important role in joint function, reducing friction during joint movement and absorbing shock, while providing flexible support. The functions of cartilage are made possible by its structure, which makes it unique among body tissues.

Microscopic Structure of Cartilage²

Cartilage is a connective tissue that is composed of two elements: cartilage cells, or chondrocytes, and the acellular matrix, which surrounds the chondrocytes and comprises about 90% of articular cartilage. Mature chondrocytes use raw materials such as amino acids, carbohydrates and water, to produce the "building blocks" of the cartilage matrix. The components of the matrix are formed within the cell and are then released from the chondrocyte into the intercellular space, where they spontaneously

self-assemble into a functional matrix.

Cartilage is an unusual tissue in that it contains no nerves, blood vessels or lymphatics. All nutrients needed by the chondrocytes are supplied by diffusion from the blood supply in the underlying trabecular bone, from the peripheral perichondrium, or from the synovial fluid. All waste products are removed by diffusion as well. This fact has important effects on the dynamics of cartilage matrix repair and maintenance. Just as cartilage is of fundamental importance to joint function, the matrix is fundamental to cartilage function; it is the microscopic and molecular structure of the matrix that gives articular cartilage its flexible resili-

GOAL: To review the anatomy, pathophysiology and pharmacotherapy of arthritic joint disease and to explore new approaches to treatment of this common problem.

OBJECTIVES: Upon completion of this article, the pharmacist should be able to:

- Describe the pathological changes in joint anatomy in osteoarthritis
- Describe the biochemical changes in cellular functions believed to be responsible for the anatomical degeneration
- Describe the principal pharmacotherapeutic approaches to therapy of osteoarthritis
- Describe the new, nonclassical interventions to provide relief of symptoms of osteoarthritis.

ient strength. Healthy joints depend upon a healthy matrix.

At the light microscopic level with routine histochemical staining, the matrix looks like a smooth homogeneous gel, but it is actually biphasic, being composed of a web of collagen fibers and the gel-like material known as “ground substance” in which the collagen fibers are embedded. Thus, the chondrocytes are surrounded and supported by their own products, the collagen fibers and ground substance that make up the matrix

Molecular Structure of the Matrix

Collagen is the single most abundant protein in the body. There are fifteen types of collagen, each distinct from the others on the basis of its molecular structure and configuration. The molecular structure of the matrix (Fig. 1) largely determines the physical characteristics of each type of collagen. Articular cartilage contains large amounts of collagen type IT and smaller amounts of collagen type DC, combined in a single rope-like fiber.

The ground substance in which the collagen fibers are embedded is composed of carbohydrates called glycosaminoglycans (GAGs), which are long chains of repeating disaccharide units (an acid sugar followed by an amino sugar). These polysaccharide molecules have numerous attached carboxyl and sulfate groups that are negatively charged at physiologic pH, and therefore give an overall negative charge to the glycosaminoglycan chain. Because of their negative charge, the polysaccharide chains strongly repel each other, and are highly hydrophilic. These physical characteristics of the GAGs are the basis for the resilient and flexible nature of cartilage as will be described.

There are six major types of GAGs present in the body: chondroitin sulfate, keratan sulfate, hyaluronic acid, dermatan sulfate, heparin, and heparan sulfate. Except for hyaluronic acid, all glycosaminoglycans are covalently bound to a linear core protein. The resulting structure is called a proteoglycan monomer (Fig. 1).

Numerous GAG chains attach to the core protein, and their negative charges cause them to be repelled by each other; resulting in a “bottle brush” configuration. In cartilage, proteoglycan monomers primarily contain two GAGs, chondroitin sulfate and keratan sulfate.

Proteoglycan monomers in turn are bound ionically to a linear molecule of hyaluronic acid, forming proteoglycan aggregates. The bonds of proteoglycan monomers with the hyaluronic acid molecule are stabilized by small link proteins. The proteoglycan aggregates intermesh and bond with the adjacent collagen fibers in the matrix (Fig. 2). In fact, the stability and functioning of the matrix depends to a large extent on the bonding between the individual GAGs (especially chondroitin sulfate), and hyaluronic acid and collagen. Collagen provides the tensile strength to cartilage and the proteoglycans provide compressive strength.³

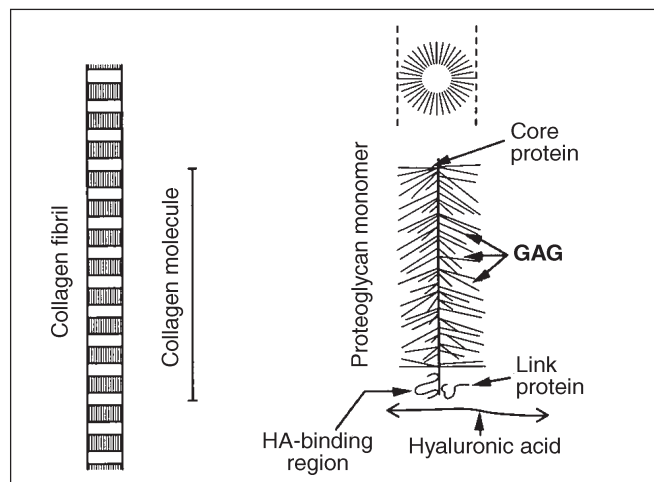
When a joint is unloaded (non-weight bearing), the matrix in the articular cartilage is not compressed, and the negative charges on the GAGs cause them to separate from each other; the negative charges also cause water present in the joint space to be drawn into the spaces between the GAGs. The linkages between collagen, the GAGs and the hyaluronic acid molecules limit the extent to which

the GAGs can separate, and therefore also limit the amount of water that can be absorbed.

This limitation is important, as excessive water in the matrix would make its consistency too soft. When the joint is loaded, the force of loading compresses the matrix, and the GAGs are pressed toward each other, thus squeezing water out of the matrix. The proximity of the GAGs to each other intensifies the electrostatic charge between them, and causes a change in the matrix pH. The pH change in turn has a stimulatory effect on the chondrocytes, causing them to make more matrix components, which is important in maintaining the matrix in the face of normal wear and tear. When the joint is unloaded, the negatively-charged GAGs soon resume their original configuration and reabsorb water. Because of its role in maintaining normal cartilage function, the importance of matrix integrity cannot be overstated.⁴

Another aspect of normal joint function that depends on normal GAGs and cartilage matrix is reduction of friction. Broadly speaking, there are two mechanisms of lubrication that occur in the synovial joint. One is “boundary lubrication.” In this mechanism, a thin film of lubricant separates two congruent surfaces. The lubricant minimizes, but does not completely eliminate, wear between the two

Figure 1. Schematic view of molecular components of cartilage



Schematic diagram presenting on the left a model of the collagen molecule and a collagen fibril, on the right a model showing the GAG molecules joined with a core protein to form a proteoglycan monomer; and showing binding sites for hyaluronic acid. (From Ross MH, Romrell LJ, Kaye GL. *Histology - a Text and Atlas*, 3rd edition, Williams & Wilkins: Baltimore, 1995.)

surfaces. In joints, this mechanism is primarily important in minimizing friction arising from the joint capsule rubbing against itself or other joint tissues. The synovial fluid produced by the synovial membrane provides this lubrication; the viscous, slimy quality of synovial fluid derives from the negative charges on the GAGs that are present in the fluid, especially hyaluronic acid.⁴ Whenever two GAGs approach each other, their negative charges repel and they “slip” past each other just as would two magnets of the same polarity.

The second mechanism of lubrication is “fluid film lubrication.” In this mechanism, in addition to the thin film of synovial fluid, lubrication is also provided by water that is squeezed out of the articular cartilage matrix as the joint is loaded. This water separates the joint surfaces and prevents virtually all wear.

Cartilage is so remarkably adapted to its purpose that joint function is practically frictionless when cartilage is normal. Problems arise when cartilage, synovial fluid, and other joint components become abnormal. Often the problem is best understood by considering what is happening at the cellular (chondrocyte) or molecular level (matrix, GAG, and collagen). Cartilage and joint dysfunction is our next focus.

Cartilage and Joint Function

The molecular and microscopic structure of cartilage enables it to reduce friction and transmit forces while absorbing shock. Because of cartilage, synovial joints can withstand tremendous forces and repetitive motions that would quickly destroy many man-made materials. However, cartilage does have limitations. All body cells, including chondrocytes, must undergo repair constantly to keep pace with breakdown that occurs in tissues during normal daily activity.

Cartilage is a relatively acellular tissue; only 10% of the volume of cartilage consists of chondrocytes. the remaining 90% is matrix. Under ideal conditions, the chondrocytes are able to produce enough matrix to maintain functionality, but any

factor that increases the ratio of matrix-loss to matrix-production will reduce cartilage health. Such factors include acute trauma, joint immobilization, inflammation, ischemia, chronic overuse, and aging.^{4,5} Exercise that is not excessive or of high-impact type is not thought to be an injurious factor.

Acute trauma occurs when cartilage or other joint structures are suddenly subjected to forces beyond their strength, such as excessive compressive loads or twisting, shearing forces. Visible fragments of cartilage may be displaced by such injuries, or ligaments may be torn, allowing the joint to assume abnormal positions. Bleeding may occur into the joint space from the joint capsule. Intra-articular haemorrhage is a source of major joint injury in haemophilic patients. Damage to the subchondral bone is also potentially serious. Because cartilage depends on the subchondral bone for support and for a portion of its blood supply, and the bone depends on its covering of cartilage for protection from the forces generated in joint movement, damage to either tissue will lead directly to injury in the other tissue. Acute trauma can also occur on the microscopic level. When shearing forces tear collagen fibers, the GAGs in the matrix are free to separate and imbibe increased amounts of water. As the matrix swells, it becomes softer and more vulnerable to further injury.⁴⁻⁶

It is easy to conceptualize how trauma injures joint tissues. Per-

haps surprisingly, immobilization can also injure cartilage. When a joint is immobilized, such as when placed in a cast, the normal cycles of loading and unloading are diminished or eliminated. When immobilization is prolonged, the resulting decrease in chondrocyte stimulation and metabolism will lead to a decrease in proteoglycan synthesis, and the articular cartilage will lose matrix. If no additional injury occurs, the cartilage can survive (and subsequently replace) a loss of up to 50% of its original matrix volume (Fig 3). This loss of matrix is responsible for the fact that articular cartilage is particularly vulnerable to injury when it returns to function after a period of immobility.

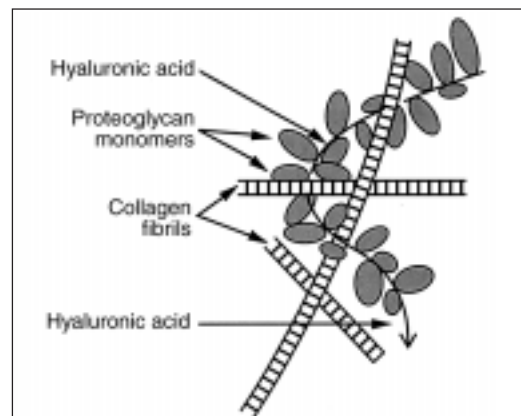
Ischemia, or poor blood supply, is harmful to any living tissue. because cartilage has no internal capillaries, it is especially vulnerable to this type of injury.

When blood supply is deficient, the chondrocytes do not receive adequate amounts of raw materials, and cellular waste products accumulate. This obviously limits the cells’ ability to produce matrix.

As previously stated, trauma to the subchondral bone can reduce blood supply. Systemic diseases such as diabetes mellitus, atherosclerosis, and heart disease can contribute to ischemia in joints as well as in other peripheral tissues.⁷

Inflammation in joints can result from septic injuries, autoimmune processes such as lupus, or as a physiologic response to injury of any kind. Within certain limits,

Figure 2. Schematic view of ground substance components



Schematic depiction showing the structure of ground substance of cartilage-hyaluronic acid with attached proteoglycans forming an aggregate with a network of collagen fibrils. (Source same as for Fig. 1.)

Table 1. Classification of Osteoarthritis

A. Primary

1. Localized (one joint or joint-group)
2. Generalized (male: female ratio = 1:10)
3. Erosive osteoarthritis (somewhat intermediate between typical OA and RA)

B. Secondary

1. Post-traumatic, acute or chronic
2. After inflammatory joint disease (e.g., RA or infectious arthritis)
3. Metabolic disorders (gout, hemochromatosis)
4. Ischemic necrosis of bone
5. Arthropathy of haemophilia
6. Congenital disorders of bone or cartilage
7. Chronic intra-articular corticosteroids

inflammation is a natural part of the healing process, but inflammation may become a self-perpetuating injurious process that leads to tissue destruction. Damaged cells may release lytic enzymes into the cartilage, synovial fluid and other articular tissues.^{6,8} Such enzymes may destroy collagen, other proteins, and GAGs, thereby intensifying and prolonging the cycle of injury. Unless kept in check, inflammation can become a major factor in some forms of joint disease.

Chronic overuse is probably the single most common factor in cartilage injury.⁸ Whether resulting from long-term overloading, as in obesity, or from repetitive motion as occurs in a baseball pitcher's shoulder, chronic overuse increases the rate of cartilage breakdown beyond the ability of chondrocytes to achieve replacement.

Aging is usually attended by a decline in joint structure and function. One reason is that as chondrocytes age, the matrix components that they produce change. In adulthood, chondrocytes produce less chondroitin sulfate and more keratan sulfate. Because keratan sulfate does not form the same tenacious linkages with collagen that chondroitin sulfate does, this change results in a matrix with less tensile strength. As aging continues, chondrocytes also produce proteoglycans with an increased proportion of dermatan sulfate, which is even less adhesive than keratan sulfate; consequently, the matrix becomes even softer and more vulnerable to injury.

The end result of these varied pathogenic mechanisms is pain

and loss of function in the affected joint, a condition usually referred to as "arthritis." However, there actually are several different types of arthritis, each having distinctive features of causation and changes produced in the affected tissues.^{6,8} The most common form of arthritis in the United States is osteoarthritis (OA), while rheumatoid arthritis (RA) is the next most common, but much less so than OA.

RA is a chronic systemic inflammatory disease that may affect many body tissues in addition to the joints. The underlying mechanism in this disease is autoimmunity.⁸ Specifically, the arthritis is an immune system-mediated attack on the synovial membrane. Its peak incidence occurs at ages 30 to 50 years, but it can begin at any age, whereas the incidence of OA rises progressively with aging. Women are three times more likely than men to be affected. Like many other autoimmune diseases, RA progresses with a fluctuating pattern of exacerbations and remissions affecting the hands and feet first, usually bilaterally, and later extending to the wrists, ankles, elbows, and knees. The hip joints and lower spine are usually spared by RA but not by OA. RA is not common, but it is a highly significant disease because it is very debilitating, and there presently is no cure. Treatments are aimed at reducing pain and minimizing the inflammatory process, sometimes by the use of agents that suppress immune functions.⁸

However, our main focus for this lesson is Osteoarthritis, also called degenerative joint disease. At times

the alternative term "osteoarthrosis" is used to indicate that its pathogenesis is not truly that of inflammatory disease, like RA, although there is likely to be secondary inflammation at some stages of the disease. OA is definitely the most common joint disease in humans (Table 1). It is primarily characterized by the progressive loss of articular cartilage. OA may result from repeated injury to joints (whether from trauma or chronic overuse) or from underlying systemic disease (such as diabetes mellitus). When there is no known initiating cause, as often is the case, the condition is called primary OA.^{4,6,8}

In some cases, OA does indeed occur in consequence to injuries to joints in earlier life - accidental trauma or chronic, low-grade injury, as from athletic activities or some types of work - but in most cases no such factor is demonstrable. There is a recent trend toward modifying the view that OA is just a degenerative response to the long-term wear-and-tear of normal activities, because a degenerative process clearly occurs despite the absence of evident provocative factors. A prime example is the OA in joints of the fingers (see Fig. 4). Thus, we must ask, what are the determining factors? Some observations suggest that there may be one or more hereditary factors of susceptibility.

A 1997 paper by Slemenda et al.⁹ turns certain suppositions about OA on their head. It has long been known that weakness of the quadriceps muscles commonly accompanies OA of the knees. It has been supposed that OA was somehow responsible for such quadriceps weakness. However, the authors hypothesized the opposite, that perhaps quadriceps weakness arises first and promotes the development of OA of the knees. Their clinical studies supported the proposition that a muscle dysfunction and quadriceps weakness may be a primary problem and a risk factor for OA of the knee.

Because of its health significance, OA has been widely studied, and much has been written about its pathogenesis. However, understanding of the exact causation of OA is so limited that some say that

it is unknown, or a mystery.⁴ The principal joints affected by OA are the knees, hips, hands, neck, and lower back. Men and women both are at risk. It typically is more slowly progressive than is RA.

Many researchers believe that degenerative changes in the cartilage appear first at the molecular level, with decreased amounts of GAGs in the matrix and a corresponding increase in the proportion of water.^{8,10} This results in a softening of the matrix termed "chondromalacia." As the characteristics of the matrix change, some chondrocytes are unable to adapt to the altered environment, and they die. Others, which are injured, or remaining unimpaired chondrocytes, may proliferate and produce an immature or abnormal collagen that weakens the matrix and contributes to a further loss of matrix strength.

The net result is a continuing diminution in the amount of articular cartilage and its ability to function. A vicious cycle is initiated, which, if unchecked, eventually may result in a complete loss of cartilage with resulting exposure of the subchondral bone. This exposed bone will proliferate because of traumatic stress, becoming more dense and producing bony projections into the joint space, which are called osteophytes. Osteophytes can limit a joint's range of motion, and can impinge on the synovial lining, causing pain. The synovial lining itself often becomes thickened with fibrovascular tissue, contributing to pain and a further limitation in the range of motion of the joint.

There are various treatments currently available that can help to reduce pain, to maximize function, and to slow the progression of the disease. These may be classed as pharmaceutical or non-pharmaceutical.

Pharmaceutical Treatment of Osteoarthritis

Drug therapy for osteoarthritis consists mainly of the non-opioid analgesics and the analgesic/anti-inflammatory drugs.⁶ Even though inflammation is not a primary

process in OA, it can contribute to pain; indeed, anti-inflammatory medications have long been considered the OA treatment of choice.¹¹

Corticosteroid Agents

Steroidal anti-inflammatory drugs may be given by a variety of routes including systemically and intrasynovially. They act by altering the regulation of protein production by a cell's nucleus. Specifically, they act to stabilize lysosomal membranes within cells, to inhibit the production of prostaglandins, to depress the function of white blood cells, and to block other inflammatory processes such as capillary dilation and fibrin deposition. Because of these actions, steroidal anti-inflammatory agents are unsurpassed at producing relief from joint pain, but unfortunately, the effect is only temporary and short-term.¹¹ Worse yet, the long-term use of corticosteroids has its own deleterious effects on joint tissue. By their very mechanism of action, corticosteroids delay normal healing. Various studies have indicated that they may adversely affect chondrocytes and their ability to synthesise GAGs.

Because corticosteroids suppress the immune response, they leave a patient more open to infectious agents. And because they reduce pain so significantly, they may actually encourage overuse of the joint. To the patient, the joint feels much improved, whereas it actually is more vulnerable to injury than

before. Generally speaking, a single dose of corticosteroids can be given without deleterious effects, but most concerned physicians recommend against their often-continuing use, e.g. more than several doses over several years.

NSAIDs

The most commonly used treatments for OA undoubtedly are the nonsteroidal anti-inflammatory drugs (NSAIDs), which class includes such familiar names as aspirin, ibuprofen, ketoprofen and naproxen, agents that are available without a prescription. Besides these, there are many more limited to prescription dispensing (Table 2). NSAIDs all share a similar primary mechanism of action - inhibition of prostaglandin synthesis. This action is believed to be the basis of their anti-inflammatory, analgesic and antipyretic effects, but it is also responsible for the side effects and hazards associated with their use.

Because NSAIDs reduce pain, they are a logical choice for the treatment of many musculoskeletal conditions, but they provide only temporary relief and do not stop the progression of OA. In fact, recent research suggests that long-term use of some NSAIDs may have steroid-like effects in depressing chondrocyte function and synthesis of GAGs.¹⁴ The various prostaglandins have wide-reaching effects in the body, and inhibiting their synthesis may cause many undesired effects. These include

Figure 3. Schematic depiction of osteoarthritic joint

Structures of a typical joint (knee showing osteoarthritic changes, with breakdown of cartilage and bone and formation of an osteophyte, a bony new growth. (From Porth CM. Pathophysiology Concepts of Altered Health States, 4th Edition, J.B. Lippincott; Philadelphia, 1995)

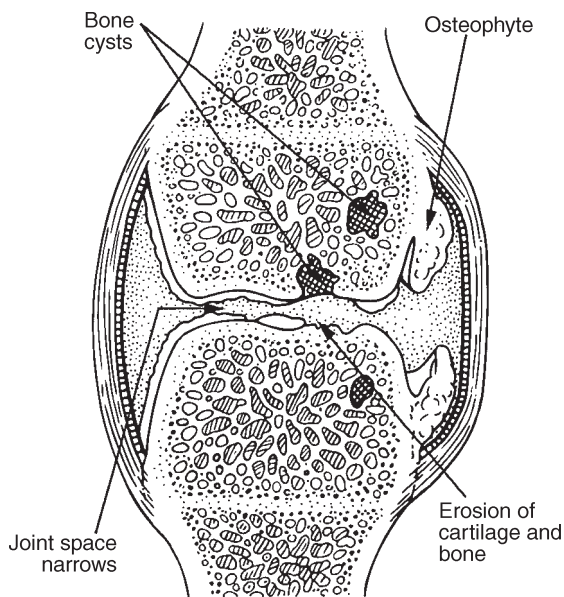


Figure 4. External view of osteoarthritic finger joints



Photograph showing osteoarthritic changes in joints of the fingers - Heberden's nodes.

especially gastrointestinal irritation that may progress to ulceration, anticoagulant effects, and renal papillary necrosis. It is said that 20% of all adverse drug reactions reported to the FDA are caused by NSAIDs. Elderly patients are at particular hazard for the occurrence of GI events that may require hospitalisation, or frank ulcerogenesis, which may become life threatening if perforation occurs. Thus, the avoidance or minimizing of NSAID use is favored by some authors who suggest the rise of the less-hazardous acetaminophen.¹⁵ Long-term high dose acetaminophen use can sometimes be hepatotoxic, and can be potentiated with heavy ingestion of alcohol. Others have recently emphasized an excess rate of hospitalisation for ulcers among elderly NSAID users. They conclude that these drugs should be used with caution in elderly persons, and alternatives to NSAID therapy should be strongly considered.¹⁶

Topical Analgesics and Counter-irritants

Topical preparations are widely used by OA sufferers.¹⁷ These comprise a diverse group of products that may include percutaneously absorbable analgesic compounds, such as methyl salicylate. Others may reduce perception of pain using the counter-irritant or rubefacient effect of menthol and/or methyl salicylate. Newer ones act by hindering function of pain pathways, the mechanism of

capsaicin-containing creams.^{17,18} However, these may cause significant burning problems in about half of the users. This group may, however, serve as a valuable adjunct to other modalities of treatment.

Nonconventional, Nondrug Treatments for Osteoarthritis

Nonpharmaceutical treatments for OA are an under-used modality.¹⁹ These treatments can reduce symptoms and are believed to slow the disease process. In addition to the so-called "chondroprotective agents, the nonpharmaceutical treatments include physical therapy (the controlled exercise of the affected joint), thermotherapy (application of heat or cold), and changes in lifestyle (weight loss, diet changes, use of various mobility aids, and stress reduction). Achieving and maintaining good control of other medical conditions, such as diabetes, and cardiac or renal disease, is also a crucial step, of course.

Viscosupplementation

Therapy

"Viscosupplementation" is the term for a therapy that aims to be chondroprotective by restoring the fluid properties of the tissue matrix in OA sufferers by means of intra-articular injections of highly purified "viscoelastic" solutions of sodium hyaluronate (HA, known also as hyaluronan) directly into the joints. Synovial fluid normally contains hyaluronic acid as a natural lubricating and cushioning agent. This substance consists of a high-molecular weight polysaccharide, which is also a common component of the extracellular matrix of diverse tissues, rather universally. In fact, the traditional biosource for HA has been cock's comb. It is also manufactured by bacterial fermentation. Both sources have similar mechanisms of action although molecular weight differs, and both appear efficacious.

Long used for treating OA in horses, HA appears to be gaining wider acceptance for human therapy. HA has seen clinical use for nearly 20 years outside the United States, mostly for OA of the knee²⁰ but also to treat periartthritis of the shoulder.²¹ This approach employs doses of 20-40 mg of a high-molecular-weight HA preparation in a sequence of 2-10 weekly

Table 2. Available Non-steroidal Anti-inflammatory Agents

Prostaglandin synthetase inhibitors

Carboxylic acids

Salicylic acids and esters

Aspirin*	S
Diflunisal	L
Salicylates*	(S-L)#

Fenamic acids

Mefenamic
Meclofenamic

Acetic acids

Indomethacin	S
Sulindac	L
Tolmetin	S
Diclofenac	S
Etodolac	S
Nabumetone	L
Ketorolac	

Propionic acids

Ibuprofen*	S
Naproxen *	L
Fenoprofen	S
Ketoprofen*	S
Flurbiprofen	S
Oxaprozin	L

Enolic acids

Oxicams	
Piroxicam	L

L = Long elimination half-life;
= Dose-dependent elimination;

S = Short half-life
* = OTC status

injections. Pain relief appears after a few days, increases progressively for a few weeks, and lasts for several months. Clinical data suggest that these benefits can endure for six to twelve months after a series of three to seven weekly injections.²⁰

Tolerance to the injection of HA is generally found to be very good. Moreover, the rate of positive response is 65% to 80% versus a 30% to 35% favorable response to vehicle (placebo) by control subjects. Compared to intra-articular corticosteroids, the benefit of HA appears to be substantially longer-lasting. Although its mechanism of action is little-known, research suggests that HA exerts more than the intended viscosupplemental effect as a physicochemical enhancer of joint fluids. Both *in vitro* and *in vivo* studies indicate that HA modulates various cellular functions; for example, it can suppress the activities of cytokines and other pro-inflammatory mediators, and it reduces the pain response in arthritic joints.²² The data suggesting a possible disease-modifying effect in animal models support the need for continued clinical studies of HA for use in OA.

An example of data supporting this therapy is from a 1996 paper relating Swedish trials on 240 patients with symptomatic, radiologically-confirmed OA of the knee.²³ They were randomly assigned to receive five weekly injections of either 25 mg of high-molecular-weight hyaluronan or a placebo. Results were gathered at seven weekly intervals, weeks 1 through 20, using visual analog scales to quantify the pain, function, motion, and activity, plus a global status evaluation by both patient and investigator.

At 20 weeks both HA and placebo groups had shown improvement compared to baseline. Comparison of HA groups stratified by age and baseline disability index showed a reliably greater benefit of HA over placebo for patients who were older than 60 years and had a higher baseline index of severity. There was no clinically relevant benefit of HA for subgroups of younger age or fewer symptoms. Patients above 60 years with OA of the knee and symptoms at a severity index of 10 or more for knee

disease were most likely to benefit.

In another study,²⁴ patients were randomized into three parallel groups: (1) NSAID continuation plus three control arthrocenteses at weekly intervals;

(2) NSAID discontinuation but with three weekly injections of a cross-linked HA preparation; and

(3) continuation of NSAID plus three weekly intra-articular injections of the HA product.

At 12 weeks all groups showed improvement from baseline, but did not differ from each other.

A test for equivalence showed that viscosupplementation gave at least equal, or greater, benefit than did continuous NSAID therapy for all outcome measures except activity restriction. In contrast to other therapies, HA had a sustained effect after treatment ceased. At 26 weeks both groups receiving HA were significantly better than a group receiving NSAIDs alone. A transient local reaction was observed in three patients after HA injection; only one patient withdrew from the study as a result and all recovered without any sequelae. One report focused on several acute negative responses to the injection.²⁵ Thus, intra-articular HA is judged to be a generally safe and effective treatment for OA of the knee that can replace or supplement NSAIDs.

Matrix Enhancement: Glucosamine and Chondroitin Therapy

The high incidence of OA and a lack of etiologic pharmacotherapy have fuelled a continuing search for new treatments that might enhance matrix synthesis and or inhibit enzymatic degradation of the matrix. The achievement of such goals would be expected to reduce joint pain and restore or improve function. The term "chondroprotective agents" came into use about 20 years ago to describe agents being sought as able to produce such ameliorative effects. The concept has called increasing attention to a dissatisfaction with the limitations and risks associated with use of NSAIDs. Compounds put forward as candidate chondroprotective agents have mainly been molecules endogenous to the joint itself: the GAGs

(chondroitin sulfate, hyaluronic acid) and glucosamine.³⁵

Glucosamine occurs naturally in the human body and is almost devoid of acute toxicity in animal studies. Thus, it is highly suitable for long-term nutritional supplementation with the aim of improving articular GAG metabolism.²⁶ It is a precursor of the GAG disaccharide unit, and therefore is a building-block of the ground substance of the articular cartilage. Furthermore, it is a component of the natural articular matrix molecule, hyaluronic acid, which is a linear, unbranched polysaccharide consisting of repeating disaccharide units of D-glucuronic acid and D-N-acetylglucosamine.

Glucosamine is essential in matrix synthesis, and it has also been demonstrated that tissue cultures of cartilage-derived fibroblasts can utilize glucosamine in their synthesis of mucopolysaccharides.²⁷ It is evidently a good substrate for the kinase that produces glucosamine-6 phosphate, which then can be used in making molecules such as hyaluronic acid. Thus, the basic concept for therapy with glucosamine is that it promotes the synthesis of those molecules essential to a healthy articular environment, which could restore a positive anabolic state in osteoarthritic joints.

Glucosamine exhibits no toxicity at high oral doses;²⁸ in studies on radio-labelled compound, it has been shown to have excellent oral bioavailability.²⁹ The primary commercial biosource of glucosamine is crustacean shells. Effective purification of the nutrient is an important consideration in processing glucosamine for oral use. Evidence is at hand that glucosamine has anti-reactive, chondrometabolic, and anti-arthritic actions in animal models.^{28,30} It has also been used in human clinical trials.³¹ It does not seem to matter what form of glucosamine is utilized. Both glucosamine HCL and glucosamine sulfate were equally effective in stimulating glycosaminoglycans in cell culture, although N-acetyl glucosamine was not as effective.²⁷

There is a wealth of information on the ability of GAGs to influence

the growth and development of cells and tissues. Chondroitin sulfate, the most abundant GAG in articular cartilage, is also present in several other mammalian tissues: tendons, bone, vertebral discs, heart valves, and cornea. Like glucosamine, CS is well absorbed orally (70% in radio-labelling studies) and has an affinity for articular tissues.³⁴

The primary function of chondroitin sulfate is to inhibit degradative enzymes that destroy cartilage. Therefore it has a protective effect which differs from the anabolic effect seen with glucosamine.

In a randomized, multicenter, double-blind, placebo-controlled study in Italy,³⁶ 146 patients with knee OA were recruited into three groups to receive either an NSAID or CS, or placebo for six months. Patients treated with an NSAID, diclofenac sodium, showed a prompt reduction of clinical symptoms, which, however, reappeared after the end of treatment. In the CS group, therapeutic response appeared later, but lasted for up to three months after the end of treatment. CS seems to produce a slow but gradually-increasing clinical benefit in OA, which lasts for a long period after stopping treatment.

In an Austrian report,³⁷ 61 patients suffering from osteoarthritis of the hip, knee and/or finger joints were included in an open, multicenter, phase IV trial. Patients were treated with CS for three months. Concomitant NSAID-therapy, necessary for symptom control at the outset of the observation period, could be lowered by 72% by the end of the three months of CS therapy. The decrease of pain was statistically significant, and no serious side effects were observed. At the beginning of the observation period patients suffered from overall severe pain; therefore, the decrease of pain to a level that could not have been achieved by NSAID therapy alone is of considerable interest. The study had a quite low drop-out rate, which eliminates a bias factor. The results of this trial demonstrated that a significant reduction of the daily NSAID consumption was possible by concomitant CS-therapy, without the

risk of deterioration of the patients condition.

A study from France included 120 patients with osteoarthritis of the knees and hips in a randomized, placebo-controlled, double-blind trial designed to evaluate the effectiveness of chondroitin sulfate.³⁸ The three-month treatment phase was followed by a two-month treatment-free phase to allow evaluation of carry-over effects. The main endpoint was the level of ad libitum intake of NSAIDs (expressed as mg of diclofenac equivalent). At completion of the treatment phase, patients taking CS were using significantly less NSAIDs. The decrease persisted throughout the two-month treatment-free follow-up phase. All other parameters studied including a visual analog pain-scale assessment, a pain-function index and overall patient and physician assessments - showed a similar significant trend. Tolerance to CS was outstanding, no patients requiring premature withdrawal. These findings show that CS is useful in treatment of OA, both as a slowly-effective agent against symptoms and by reducing the need for NSAIDs. The early-over effect of CS suggests that intermittent administration may be appropriate.

Another compound that is often used with glucosamine and chondroitin is manganese. Manganese is a trace element that naturally occurs in some foods and is present in the body as well. It is an important cofactor in the biochemical reactions by which joint tissues are made. Specifically, the reactions that make glycosaminoglycans out of glucosamine will not occur efficiently unless manganese is present in the body.³⁹ For the estimated 37% of Americans who are marginally deficient in manganese,⁴⁰ these reactions will occur at a limited rate. Supplementing manganese helps ensure that GAG synthesis occurs at the maximum possible rate. Manganese ascorbate is a well absorbed salt compound of manganese and ascorbic acid (or vitamin C), which is itself a necessary co-factor in the synthesis of collagen.

In summary, used individually, both CS and glucosamine have

been found by various European researchers to be effective in reducing symptoms of OA without adverse side effects. The combining of glucosamine with a GAG, chondroitin sulfate (CS), arises from the concept that CS, like other GAGs, not only has a critical structural role, but also has important regulatory functions in various tissues, presumably including joints.³² Many animal studies completed in the United States on the combination of glucosamine HCl, chondroitin sulfate, and manganese have shown a positive clinical effect.⁴¹⁻⁴⁶ Double-blind, randomized, placebo-controlled clinical trials are continuing in the United States to further validate the combination of glucosamine HCl, CS, and manganese ascorbate.

When given in combination, glucosamine and chondroitin sulfate provide a synergistic effect in forming GAGs, inhibiting degradative enzymes, and up-regulating cartilage metabolism. This synergistic effect has been documented in cell culture studies.⁴⁸ The net result may be expected to be enhanced health of articular cartilage matrix.

A patented oral product combining therapeutic amounts of the chondroprotective agents glucosamine (500 mg, as the hydrochloride), purified chondroitin sulfate (400 mg), and manganese ascorbate (76 mg) is currently available. The recommended daily dosage is 3 capsules; 2 capsules in the morning and 1 capsule in the evening for the first 60 days. After 60 days, dosage may be lowered gradually, depending on the patient's response. Clinical trials are now underway on this patented combination and are said to be yielding positive results.⁴⁷ A recent article from Johns Hopkins University reported "Special attention focuses on oral chondroprotectives, and extensive research supports the concurrent use of oral glucosamine and chondroitin sulfate."⁵⁰

Concerning chondroprotective therapy, two points need to be remembered. Firstly, because these must act via living chondrocytes, they are likely to be most effective if used early in the course of the disease, when viable chondrocytes and some cartilage remain over

joint surfaces. Also, because these agents are nutrients, not pharmaceuticals, a response should not be expected to occur immediately, and full effect may not be seen until 6 to 8 weeks of therapy are completed. Another issue that must be considered is the purity of the compounds. All of the research that has been conducted has used pharmaceutical grade glucosamine and chondroitin sulfate. In fact, recent information from the University of Maryland School of Pharmacy has indicated that a large percentage of products may not meet label claim.⁴⁹ It is, therefore, important to use a source from a reputable company that subjects their product to pharmaceutical GMP quality control and clinical studies.

As the average age of the population increases, osteoarthritis will increasingly be an important cause of pain and disability for added millions of people. It is a disease in which a variety of therapies can be used to minimize symptoms and maximize quality of life. The optimal treatment protocol will vary depending on the health needs, finances, and personal preference and tolerance of each individual. As strategically-located members of the health-care team, community pharmacists are ideally placed to fully inform their clients of the options that are available, and to aid them in choosing the best treatments for their individual circumstances.

REFERENCES

1. Tortora G J, Grabowski SR, eds. Articulations. in: Principles of Anatomy and Physiology 7th ed. New York: Harner and Collins; 1993.
2. Hildebrand M. Analysis of Vertebrate Structure. 2nd ed. New York: John Wiley and Sons; 1982.
3. Goldberg B, Rabinovitch M. Connective tissue. In: Weiss and Greep, eds. Histology 4th ed. New York: McGrawHill; 1977.
4. Martin DE. Pathomechanics of knee osteoarthritis. Med Sport Exercise 1994;26:1429-1434.
5. Sokoloff L. The biomechanics of osteoarthritis. In: The Biology of Degenerative Joint Disease. Chicago: University of Chicago Press; 1969.
6. Porth CM. Alterations in skeletal support and movement. to: Pathophysiology-Concept of Altered Health States 4th ed. Philadelphia: Lippincott; 1994.
7. Kellgren JH. Osteoarthritis in patients and populations. Br Med J 1961; 2:5243-5248.
8. Rosenberg AE. Skeletal system and soft tissue tumors. In: Robbins Pathologic Basis of Disease. 5th ed. Cotran RS, Kumar V, Robbins SL, eds. Philadelphia: Saunders; 1994.
9. Slemenda C, Brandt RD, Heilman OK, Mazzuca S, Braunstein EM, Katz BR Wolinsky FD. Quadriceps weakness and osteoarthritis of the knee. Ann Intern Med 1997;127:97-104.
10. Mankin H J, Lippiello L. The glycosaminoglycans of normal and arthritic cartilage. J Clin Invest 1971; 50:1712-1719.
11. Spencer-Green G. Drug treatment of arthritis: update on conventional and less conventional methods. Postgrad Med 1993;93(7):129-140.
12. Brooks PM, Day RD. Nonsteroidal anti-inflammatory drugs - similarities and differences. N Engl J Med 1991;324:1716-1725.
13. Al Arfag A, Davis P. Osteoarthritis 1991-current drug treatment regimens. Drugs 1991;41:193-201.
14. Paimoski M, Brandt K. Effects of some nonsteroidal anti-inflammatory drugs on proteoglycan metabolism and organization in canine articular cartilage. Arthritis Rheum 1980;23:1010-1020.
15. Cicuttini FM, Spector TD. Osteoarthritis in the aged. Epidemiological issues and optimal management. Drugs Aging 1995; 6:409-420.
16. Smalley WE, Ray WA, Daugherty JR, Griffin MR. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. Am J Epidemiol 1995; 141: 539-545.
17. Griffin MR, Brandt KD, Liang MH, Pincus T, Ray WA. Practical management of osteoarthritis. Arch Fam Med 1995;4:1049-1055.
18. Cerinic MM, McCarthy G, Lombardi A, Pignone A, Partsch G. Neurogenic influences in arthritis: Potential modification by capsaicin. J Rheum 1995; 22:1447-1449.
19. Pinals RS. Pharmacological treatment of arthritis. Clin Ther 1992; 14:3336-3347.
20. Peyron JG. Intra-articular hyaluronan injections in the treatment of osteoarthritis: state-of-the-art review. J Rheumatol 1993; suppl.39:10-15.
21. Itokazu M, Matsunaga T. Clinical evaluation of high-molecular-weight sodium hyaluronate for the treatment of patients with periartthritis of the shoulder. Clin Ther 1995;17: 946-955.
22. Goa KL, Benfield P. Hyaluronic acid: A review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound healing. Drugs 1994;47:536-566.
23. Lohmander LS, Dalen N, Englund G, Hamalainen M, Jensen EM, Karlsson K, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: A randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. Ann Rheum Dis 1996;55:424-431.
24. Adams ME, Atkinson MH, Lussier AJ, Schulz JI, Siminovitch KA, Wade JP, Zummer M. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: A Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis-Cartilage 1995;3:213-225.
25. Purtick MP, Wade JR, Chalmers A, Cornell DG, Rangno KK. Acute local reactions after intra-articular hylan for osteoarthritis of the knee. J Rheumatol 1995;22:1311-1314.
26. McCarty MF. The neglect of glucosamine as a treatment for

- osteoarthritis a personal perspective. *Med Hypoth* 1994;42:323-327.
27. Karzel K, Domenjuz R. Effects of hexosamine derivatives and uronic acid derivatives on glycosaminoglycane metabolism of fibroblast cultures. *Pharmacology* 1971;5:337-345.
 28. Setnikar I, Cereda R, Pacini MA, Revel L. Antireactive properties of glucosamine sulfate. *Arzneim-Forsch* 1991;41:157-161.
 29. Setnikar IG, Giachetti C, Zanolio G. Pharmacokinetics of glucosamine in the dog and in man. *Arzneim-Forsch* 1986;36:729-735.
 30. Setnikar I, Pacini MA, Revel L. Antiarthritic effects of glucosamine sulfate studied in animal models. *ArzneimForsch* 1991;41:542-545.
 31. Fassbender HM, Bach GL, Haase W, Rovatis LC, Setnikar I. Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. *Osteoarthritis and Cartilage*, 1994; 2: 61-69, The Osteoarthritis Research Society.
 32. Paroli E. Glycosaminoglycan chondroprotection: Pharmacological vistas. *Int J Clin Pharmacol Res.* 1993;13 suppl:1-9.
 33. Templeton DM. Proteoglycans in cell regulation. *Crit Rev Clin Lab Sci* 1992;29:141-184.
 34. Conte A, Volpi N, Palimeri L, Bahous I, Ronca G. Biochemical and pharmacokinetic aspects of oral treatment with chondroitin sulfate. *Arzneim-Forsch* 1995;45:918925.
 35. Bucci, LR, Chondroprotective agents, glucosamine salts and chondroitin sulfates. *Townsend Letter for Doctors*, January 1994.
 36. Morreale R, Manopulo R, Galati M, Boccanera L, Saponati G, Boccin L. Comparison of the anti-inflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. *J Rheumatol* 1996;23:1385-1391.
 37. Leeb BF, Petera R, Neumann K. [Results of a multicenter study of chondroitin sulfate (Condrosulf) use in arthroses of the finger; knee and hip joints. (In German)] *Wien Med Wochenschr* 1996;146:609-614.
 38. Mazieres B, Loyau G, Menkes CJ, Valat JP, Dreiser RL, Charlot J, MasounabePuyanne A. [Chondroitin sulfate in the treatment of gonarthrosis and coxarthrosis: 5-months result of a multicenter double-blind controlled prospective study using placebo. (In French)]. *Rev Rhum Mal Osteoartic* 1992;59:466-472.
 39. Leach, RM (1971): Role of manganese in mucopolysaccharide metabolism. *Fed Proc.*, 1971; 30(3):991.
 40. Freeland-Graves JH, Bales CW, Behmardi F: Manganese requirements of humans. In: *Nutritional Bioavailability of Manganese*. Kies C, ed., Washington: American Chemical Society; 1987: p.90.
 41. Hulse DS, Hart D, Slatter M, Beal BS. The effect of cosequin in cranial cruciate deficient and reconstructed stifle joints in dogs. *Texas A & M Univ., College Station, TX and Gulf Coast Veterinary Specialists, Houston, TX, Veterinary Orthopedic Society, 25th Annual Conference, February 21-28, 1998, Snowmass, CO.*
 42. McNamara PS, Barr SC, Erb HN. Hematologic, hemostatic, and biochemical effects in dogs receiving an oral chondroprotective agent for thirty days. *American Journal Veterinary Research.* 57: 9:1390-1394, 1996.
 43. Baron J, Hill SL, Rose Nit. Therapeutic effect of Cosamin® on autoimmune type II collagen induced arthritis in rats. *Proceedings of North American Veterinary Conference (Innovations And New Product Applications In Veterinary Practice)*, page 35, January 1997.
 44. Hanson RR, Hammad TA, Brawner WR. Evaluation of the clinical efficacy of cosequin in the treatment of navicular syndrome- a double-blinded placebo controlled randomized clinical trial, 1997. *ACVS Veterinary Symposium Small Animal Proceedings*, pages 9-10, October 16-19, 1997.
 45. Anderson M, Slater M, Hammad TA, Results of a survey of small animals practitioners on the perceived clinical efficacy and safety of an oral chondroprotective nutraceutical, 1997. *ACVS Veterinary Symposium Small Animal Proceedings*, page 1, October 16-19, 1997.
 46. Hanson RR, Smalley LR, Huff GK, White S, Hammad TA, Oral treatment with a glucosamine-chondroitin sulfate compound for degenerative joint disease in horses: 25 cases. *Equine Practice.* 19:9, October 1997.
 47. Brody JE, The Arthritis is at Bay, Thank You., *The New York Times.* January 13, 1998, C9.
 48. McNamara PS, Bar SC, Idouraine A, Lippiello L. Effects of an oral chondroprotective agent (Cosequin) on cartilage metabolism and canine serum. *Proceedings of the 24th Annual Conference of the Veterinary Orthopedic Society.* 1997; page 35.
 49. *Newsweek*; February 17, 1997, p. 54.
 50. Hungerford D, Treating osteoarthritis with chondroprotective agents. *Orthopedic Special Edition*, 4:1:39-42, 1998.

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