

Our Participants



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Michael W. Orth, PhD, is an associate professor of skeletal biology, Department of Animal Science, Michigan State University, East Lansing, Michigan.



Nathaniel A. White II, DVM, MS, DACVS, is the Jean Ellen Shehan Professor and Director, Marion duPont Scott Equine Medical Center, Leesburg, Virginia.

Glycosaminoglycan (GAG) therapy involving the use of chondroitin sulfate (a GAG) and glucosamine (an amino sugar) is administered to mediate or prevent the progressive deterioration of articular cartilage, known as degenerative joint disease (DJD). Research on these compounds is ongoing and seeks to prove their modes of action, efficaciousness, and most effective combination(s) and route(s) of administration. In the meantime, numerous products containing many different glucosamine–chondroitin sulfate combinations are being marketed as joint supplements. These products, which sometimes also contain various other compounds, make wide-ranging claims of efficacy, most of which have not been substantiated.

The intent of this roundtable is to describe the current state of GAG therapy as it pertains to equine DJD, including its use and effectiveness, and to dispel some of these unsubstantiated claims.

Osteoarthritis: Pathophysiology and Patient Assessment

Elizabeth P. Boulton, DVM, DACVS (Moderator): What is the pathophysiology of osteoarthritis in horses, and how is osteoarthritis graded?

Nathaniel A. White II, DVM, MS, DACVS: Osteoarthritis begins when wear and tear, an acute

traumatic incident, or sepsis causes cartilage damage. The affected joint becomes inflamed, which can become a cyclic event in that once there is damage to cartilage or even to the synovial lining, the inflammatory process interrupts nutrition to the joint. The chondrocytes and synoviocytes participate in the inflammatory process, which ultimately causes the breakdown of cartilage. The inflammatory process of the synovial lining and the cyclic event eventually lead to further degeneration, which is called *degenerative joint disease* (DJD). The pathophysiology of DJD is quite complicated, as there are roles for the cells, cytokines, and humoral responses of the body.

How osteoarthritis is graded depends mostly on the individual horse, its discipline, and its tolerance of pain. A high-level performance horse probably does not need much osteoarthritis to affect his performance. On the other hand, a field hunter may be able to perform with some degenerative changes or low-grade arthritis. The lameness associated with DJD is normally graded on a scale from 1 to 5, with grade 1 being mild lameness and grade 5 representing a horse that has non-weight bearing lameness.

Boulton: What sort of clinical criteria do you consider when evaluating a horse for osteoarthritis?

Paul C. Mountan, DVM: You try to determine whether there might be soft tissue injuries. This is done by

palpating the horse and getting a good history. A horse that has been performing in demanding events such as upper-level dressage or cutting for a few years is probably going to have some osteoarthritis in the lower hock joints. Flexion tests are helpful in evaluating joint problems.

If a horse has pain in its hock, I try something like Cosequin (Nutramax Laboratories, Inc.). If I later find that the horse still isn't performing well, I go back and reevaluate the horse to make sure I didn't miss anything else like a foot abscess, a bruise, or a sprained suspensory ligament.

R. Reid Hanson, DVM, DACVS, DACVECC:

We start off by checking to see if the horse is lame and then use different modalities to determine the source of the lameness. We do a presentation history. We then perform an orthopedic exam, including a physical exam that concentrates on the legs. After that, we use hoof tester evaluation, responses to flexion tests, and lunging. If the clients are there and we think it will add to the exam, we have the rider get on the horse and do part of the evaluation with the rider up. Based on that, we develop a diagnostic plan that includes regional local anesthesia to parts of the leg to try to isolate the lameness. Depending on these findings, we then use either radiography, ultrasonography, or, in some cases, nuclear scintigraphy or computed tomography.

Mechanism of Action of Glycosaminoglycans

Boulton: *Sometimes GAGs are referred to as disease-modifying agents. Do you place them in this category?*

Hanson: GAGs have some, but not all, of the properties of disease-modifying agents. Disease-modifying agents have several effects, including increasing the synthesis of hyaluronic acid, decreasing the concentration of inflammatory mediators in the joint, and increasing the synthesis of molecular aggregans. The effects of these agents depend on the cascade of events. If the cascade of events that result in synovitis can be arrested, it may be possible to prevent damage to the articular cartilage and subchondral bone. This requires regulating the synthesis of inflammatory cytokines and metalloproteinase enzymes.

White: The GAGs can modify the early inflammatory stage of osteoarthritis, stabilize the cartilage to some extent, and alter the clinical signs. If the problem is

severe enough, the disease can progress even in the face of this form of therapy. So the GAGs may modify the clinical signs, but depending on the severity of the disease, these compounds by themselves can't change the final course of the disease.

Michael W. Orth, PhD: Much of the research that has been performed has involved in vitro studies using equine and bovine cartilage explants and cells. Some of the early studies in this area were undertaken before we could accurately measure the concentration of chondroitin sulfate in the blood. As a result, concentrations that were used in vitro exceeded what actually occurs in circulation.

More recently, we have tested the effects of chondroitin sulfate concentrations that have been measured in the blood to see how they affect gene expression patterns and concentrations of some of the inflammatory mediators, such as nitric oxide and prostaglandin E₂. Quite a bit of literature indicates that chronic production of these inflammatory mediators can be damaging to articular cartilage. We have found that the specific glucosamine and chondroitin sulfate found in Cosequin arrest the production of some of those mediators. They seem to be the most effective when combined rather than when used individually. At the same time, expression of the genes for the matrix metalloproteinases (MMPs)—the enzymes involved in degrading the cartilage matrix—is reduced, as is the activity of those enzymes. The expression of the genes for some of the natural inhibitors of the MMPs is increased. Specifically, TIMP-3 [tissue inhibitor of metalloproteinase 3] is increased in bovine articular cartilage explants cultured with glucosamine and chondroitin sulfate.

Boulton: *So how important is it that glucosamine be used in combination with a low-molecular-weight chondroitin sulfate?*

Orth: Based on our research findings, it does seem to make a difference if the two compounds are used together. Glucosamine likely enters cells through glucose transport mechanisms. As a result, glucosamine can exert its effects intracellularly. On the other hand, chondroitin sulfate is probably interacting at the level of cell surface receptors. In our research, the combination of the two has the most pronounced effects at the level of gene expression, especially on inhibition of nitric oxide production.

Boulton: Can the clinical relevance of bovine explant research be applied to equine explants?

Orth: I think in a general sense it can. In human research, people working at the cellular or molecular level use bovine cartilage for two reasons: the ease of getting tissue and the amount of data you can collect from a large pool of tissue. Research has been performed using cartilage from dogs, rabbits, cattle, and horses, and the results are generally very similar, with only subtle differences between species. However, when

we have looked at prostaglandin E₂ or nitric oxide production and some of the MMPs, we haven't found any differences. Side by side, bovine and equine studies yield comparable results.

Treatment Protocols

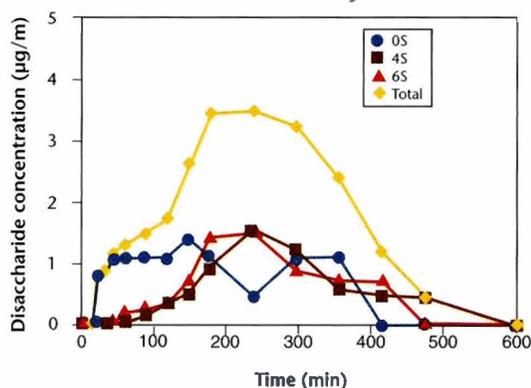
Boulton: When do you use an injectable agent versus an oral agent? Do you ever use the two together?

Mountan: If I have a horse with osteoarthritis, I usually start by administering oral chondroprotectives in combination with some NSAIDs. Depending on the level of work the horse is doing, if that combination doesn't provide sufficient relief, I reevaluate the situation. Depending on the client's expectations for the horse, I add injectables if needed. If the combination approach of oral and injectable agents doesn't work, I consider using intra-articular injections. If the horse is of Olympic (high-level) caliber, the move to the injectable agents usually occurs more rapidly. Fortunately, the combination of oral and systemically injectable agents usually works, which reduces the need to inject agents directly into the joint. This is a good thing for the horse, the owner, and even the veterinarian.

Relevant Research: Evidence for Oral Absorption of Glucosamine and Chondroitin Sulfate in Horses

Du J, White N, Eddington ND: The bioavailability and pharmacokinetics of glucosamine hydrochloride and chondroitin sulfate after oral and intravenous single dose administration in the horse. *Biopharm Drug Dispos* 25:109-116, 2004.

Total and individual disaccharides (Δ Di-0S, Δ Di-4S, Δ Di-6S) after administration of TRH122 chondroitin sulfate PO (3 g) to one of the study horses



Objective: To determine if TRH122 low-molecular-weight chondroitin sulfate and FCHG49 glucosamine hydrochloride, as found in Cosequin, are orally absorbed in horses.

Methods: Bioavailability was determined in 10 adult horses administered TRH122 low-molecular-weight chondroitin sulfate and FCHG49 glucosamine hydrochloride either intravenously or orally.

Results: Both TRH122 low-molecular-weight chondroitin sulfate and FCHG49 glucosamine hydrochloride were absorbed when given orally.

White: I hardly ever use oral glucosamine and chondroitin sulfate alone. In our referral hospital, we often use the injectable agents in horses after surgery for severe joint disease. We often combine oral therapy with another type of agent that is injected into the joint, either cortisone or hyaluronic acid, and then follow up with oral glucosamine and chondroitin sulfate long term.

If a disease has a chronic onset, chronic progression, and chronic history, we find that we get a better response with the oral glucosamine-chondroitin sulfate combination. The combination doesn't necessarily eliminate the disease or the lameness, but it returns the horse to a certain level of soundness. Depending on the lesion, we usually start with an intra-articular medication to arrest the initial inflammation, regardless of whether the inflammation is a result of severe capsulitis-synovitis or chronic arthritis or is secondary to surgery.

Clients come to the hospital to get results. They are not coming to have their horse lame 2 weeks from now. So we usually start the horse on NSAIDs for 3 to 4 days after the joint injection until that medication takes effect. If the clients are not in a tremendous hurry,

we use the oral compounds. If the clients want results quickly, we add injectable disease-modifying agents in addition to the oral therapy.

There are two chronic conditions that we seem to have good response with: navicular syndrome and bone spavin. We see a lot of that in our practice area. In horses without a lot of radiographic changes to the foot and with normal, balanced shoeing, the oral combination alone modifies the lameness enough that the client is happy with the horse's performance. Sometimes we combine the oral therapy with joint injections initially, depending on the severity of the lameness. A lot of horses with bone spavin that receive the joint injections—either alone or in combination with oral treatment—will improve for 2 to 4 months, although many never quite achieve the level of soundness that the client would like. However, we have found that the combination of joint injections and continuous oral dosing reduces the lameness another half grade or so, allowing the horse to be a functional athlete.

Boulton: *Do you feel it takes a couple of weeks before you see a positive effect with oral glucosamine and chondroitin sulfate? How long do you use these products before you switch to something else?*

White: We did a preliminary blinded study with Cosequin in a model of chronic fetlock disease. It was a cartilage particle model that mimicked the effects of trauma and wear and tear on the joint. Generally, the horses were comfortable walking but were lame when they were trotted in a circle. Although there were only two horses in each group, we found that two of the horses had improved after 4 to 5 weeks and the other two horses remained lame. At about 3 months, we had two sound horses while the other horses had improved a bit but were still lame. When we finally broke the code, we found that the two sound horses had been treated with Cosequin.

We did not see an immediate effect with these compounds in that model, nor do I think we should expect to. I think time is really important. The initial aim should be to break the inflammatory cycle as best we can right away and then maintain the benefit by administering the oral compounds over a long period of time.

Based on this study, I think you need to wait a couple of months to see a full effect. We did see a change in 2 to 3 weeks, which leveled out at about 2 months. That study went for 16 weeks, and the

positive effects were maintained. When the project was over and we were able to examine the joints grossly and with histology, in our model, neither group showed significant cartilage wear. However, there were differences in the clinical signs.

The initial aim should be to break the inflammatory cycle and then maintain the benefit by administering the oral GAGs over a long period of time.

Mountan: Clinically, I see a quicker response than what Dr. White saw in his model, but probably my cases are a lot less severe. We usually see a beneficial effect within 2 weeks to a month, even with the injectables. It depends on what the animal is doing and what the owner's expectations are. If the horse is a field hunter or a pleasure horse, we'll often use oral glucosamine and chondroitin sulfate for a few weeks. At the same time, we make sure the horse has proper shoeing and trimming. If the horse was going to a high-level competition, the time frame might be shorter.

Hanson: It is difficult to produce a model for chronic DJD in horses. Many of the models that have been used are synovitis or inflammatory joint models. As a result, problems arise when you try to apply results from those studies to clinical cases of chronic-use DJD. Depending on the disease process that is causing the lameness, if the underlying cause of the clinical signs is more than inflammation and soft tissue swelling, you may see different responses than if you are dealing with a chronic low-grade lameness condition. Until we can produce a reliable model for chronic DJD, I think we will have to extrapolate the results that do exist to different clinical scenarios.

We did a nonblinded clinical trial that included 25 horses with various forms of natural progression of DJD from the fetlock to the coffin joint to the hocks.¹ The owners and veterinarians evaluated the responses. The most significant changes occurred within the first 2 weeks of the product being given, with improvements noted in lameness scores, stride length, and flexion tests. There was still significant improvement in lameness at 4 weeks.

Boulton: Do you see differences between the various disciplines as far as response to the oral GAGs and the involved joints? Do you use different treatment protocols depending on whether it is a pleasure horse or a performance horse?

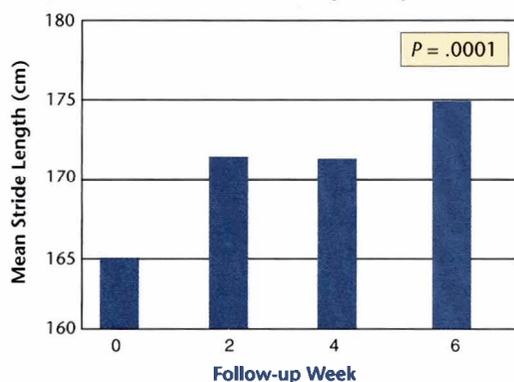
Mountan: I think oral GAGs help in all the disciplines. Of course, the different disciplines stress different parts of the body, to varying degrees. The dressage horses work off their hocks a lot. When they are given oral GAGs, their extensions and overall movement are

better. Cutting horses really use their hocks, too. Many of those horses are on the oral GAGs. In some cases, we inject their hock and stifle joints with hyaluronic acid and steroids before they go to their competitions. It's the same with the show hunters. They also use their hocks a lot. Sometimes, if a horse misses one lead change in a show, the horse is instantly scheduled for hock joint injections. For show hunters to win their hack classes, they have to move smoothly from the shoulder. If they have any coffin joint pain or navicular pain, they have shorter strides and never win the flat

Relevant Research: Efficacy of Cosequin in Horses

Hanson RR, Smalley LR, Huff GK, et al: Oral treatment with a glucosamine–chondroitin sulfate compound for degenerative joint disease in horses: 25 cases. *Equine Pract* 19(9):16–22, 1997.

Mean Stride Length of 25 Horses with DJD after Administration of Cosequin Equine Powder



Objective: To evaluate the efficacy of Cosequin in horses with DJD.

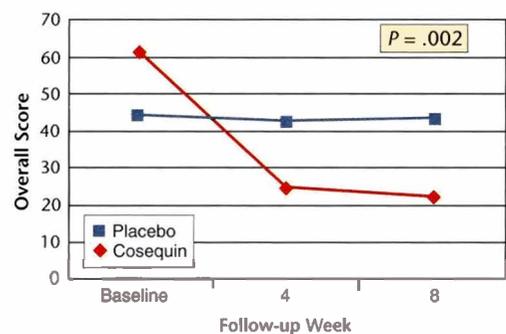
Methods: Twenty-five horses with radiographically or fluoroscopically confirmed evidence of DJD of the hock, fetlock joint, or pastern joint were administered Cosequin Equine Powder as per label directions based on body weight twice daily for 6 weeks. Every 2 weeks, lameness grade, flexion, and stride length were measured.

Results: A significant improvement in all parameters was noted at week 2.

Conclusion: A significant improvement was noted regardless of age, joint affected, or discipline of the horse. Some of the horses returned to competition after 2 weeks of Cosequin administration.

Hanson RR, Brawner WR, Blaik MA, et al: Oral treatment with a nutraceutical (Cosequin®) for ameliorating signs of navicular syndrome in horses. *Vet Ther* 2(2):148–159, 2001

Mean Overall Clinical Condition Score by Investigator



Objective: To evaluate the efficacy of Cosequin in improving signs associated with navicular syndrome in horses in a randomized, double-blind, placebo-controlled study.

Methods: Fourteen horses ranging in age from 5 to 15 years with a history of progressive forelimb lameness for 3 to 12 months were administered five scoops of Cosequin Equine Powder or placebo twice daily for 2 months. Horse owners and a veterinary investigator assessed lameness scores and overall clinical condition scores.

Results: Median lameness and overall clinical condition scores as rated by the veterinary investigator were significantly improved in the group administered Cosequin versus the group given a placebo.

Conclusion: The investigator concluded that Cosequin supplementation was effective in these horses.

hack classes. I think adding the GAGs significantly cuts down on the number of injections needed.

We definitely base our treatments on the discipline and the level of competition. The show hunters and the dressage horses have to be really sound when trotting in circles. The field hunters and the pleasure horses just have to be comfortable and safe. Their hocks have to feel good enough so they are not refusing or stumbling over jumps. Polo ponies are in between, because they don't have to trot in circles but they have to be able to stop and turn quickly and gallop hard.

White: Racehorses commonly have the front fetlocks and carpi affected because of the stress applied to these joints during racing. Standardbred racehorses also suffer from hock lameness; hock and stifle lameness are less common in thoroughbreds.

I think that in racehorses, we are dealing with subchondral bone injury almost as much as the cartilage injury. So we treat the joint, but we also have to contend with the bone. During joint treatment, rest is critical in many of these cases to allow the bone to heal. Whether it is a sport horse, a pleasure horse, or a racehorse, we need to remember that we are treating all parts of the joint. For example, if the horse has synovitis, we treat the synovitis. If the horse has a chip fracture, we have to take care of that. The difference is that in many instances, the racehorse has concurrent subchondral bone pain and is lamer and may need more rest. I think what works is to look at the joint, consider the horse's breed and discipline, and ask, "What does this individual horse need?"

Glycosaminoglycans for Protection and Prevention

Boulton: Do you keep horses on the oral GAGs long term? Indefinitely? Do you use them prophylactically?

White: We certainly use oral GAGs in surgical cases if we have a joint that looks like it needs anti-inflammatory therapy long term. I really think that the treatment needs to be long term to get the full benefit. As far as using oral GAGs prophylactically, one of my clients kept every one of his racehorses on them all the time. The horses still got chip fractures. They still got arthritis. Does anybody have any evidence that oral GAGs act as a protectant in horses? I don't think they do, but I don't know of any proof that they don't.

Mountan: I use oral GAGs over the long term—months after the injury or infection occurs, while the horse is convalescing, in stall rest, and hand walking. Then if the horse is turned out and is doing fine, I might stop the oral GAGs.

We use oral GAGs prophylactically, as do a lot of our clients. Again, we've got everything from foals to old field hunters. I guess you do see more response in the older, semiarthritic horses, but I don't see how using oral GAGs prophylactically could hurt if a young horse's joints are being stressed.

Boulton: Can you use a product prophylactically and change gene expression to protect joints?

Orth: In a lot of the human studies, the benefits of glucosamine and chondroitin sulfate are seen primarily in people with mild osteoarthritis. The concept to keep in mind is that of a stressed joint, with glucosamine-chondroitin sulfate being a stress modifier. So if you have an animal that is in a point of stress but does not necessarily have a disease, I think the compounds could have a benefit. From a scientific standpoint, many of the studies using animal models begin with joints that have normal cartilage at the start that degrades over time. If you look at these studies, the compounds are being evaluated prophylactically to see if they can modify, for example, the effects of cutting an anterior cruciate ligament or performing a meniscectomy. So in essence, the compounds are being used prophylactically to determine if they can avoid the damage. I think there are some legitimate reasons and benefits to using the compounds if you know your animal is going to be stressed by its physical activity.

Boulton: How do you determine how long to use a loading dose and when to switch to the maintenance dose? If you don't see an effect even on the loading dose, have you ever increased the dose?

Mountan: I usually follow the manufacturer's recommendations. However, I use whatever works for a particular horse. If I'm not getting a positive effect at the maintenance dose, I put the horse back on the loading dose. Often, I see a big improvement with this.

White: If we have a horse postsurgery and we decide to use oral therapy, we use a loading dose for the entire treatment. If we assume that the compounds are able to stop an inflammatory response or allow the

cartilage to be repaired, then it makes sense to use a dose that has the greatest chance of achieving these results. We find that owners stop using the compounds when they don't get the results they want, for instance, when the lameness or injury is severe.

If we have a really big horse, such as some of the 1,500- to 1,600-lb Warmbloods that we see, we increase the amount of Cosequin from three scoops to four or five scoops. Based simply on their large size, we assume a large horse needs more.

Hanson: I tend to use a high dose for the first month of treatment. I think that if you are going to get a response, it will probably occur in the first month. Rather than giving the label dose, I use the compound at a higher dose to see if we can arrest the clinical signs and get the horse moving better. If we get to that point, we can decrease the initial dose after the first 30 days and then determine the maintenance level. I think different horses respond differently, and part of this response depends on the specific diseases. And even with the same disease, different horses can require different dosing regimens.

Boulton: *Do you avoid having to refer some of your cases because you're able to obtain positive results with the oral compounds?*

Relevant Research: Use of Cosequin under Conditions of Joint Stress

Lippiello L: Glucosamine HCl and chondroitin sulfate: Biological response modifiers of chondrocytes under simulated conditions of joint stress. *Osteoarthr Cartil* 11(5):335-342, 2003.

Objective: To evaluate the response of chondrocytes to FCHG49 glucosamine hydrochloride and TRH122 low-molecular-weight chondroitin sulfate (LMWCS), as found in Cosequin, under simulated conditions of joint stress.

Methods: Bovine cartilage explants were cultured under the following four conditions: (1) stress induction by cartilage matrix depletion, (2) stress induction by heat stress, (3) stress induction by cytokines, and (4) stress induction by mechanical compression. Effects of glucosamine hydrochloride and LMWCS, alone and/or in combination, on cartilage production and degradation caused by these stressors were measured.

Mountan: Definitely. An event horse was sound for a couple of years and then went extremely lame. I was sure it had an abscess. When the horse didn't get better, we took radiographs and saw a cyst about the size of a nickel in the second phalanx that communicated with the pastern joint. Surgery wasn't an option, so we used Cosequin, injectable GAGs, NSAIDs, and rest. The horse came back and performed well. The treatment definitely helped. The more of the GAGs that the horses get, the better they are; it heals the cartilage and keeps the horses happy.

Boulton: *Can you use oral GAGs in place of osteochondritis dissecans (OCD) surgery and still have a positive outcome?*

White: That all depends on the disease. If it is mild and you are altering the lameness and reducing inflammation, I think the oral GAGs can be used that way. Using OCD as an example, you need to ask yourself, could you use the oral GAGs and would they substitute for surgery? In a mild case, they might. And could you use them in a younger horse and perhaps encourage the lesion to heal while resting the horse and using other treatments such as injectable GAGs or hyaluronic acid? Oral glucosamine and chondroitin sulfate have the potential to help reduce inflammation,

Results: A difference was noted in the response of cartilage from aged versus young animals to the various simulated conditions of joint stress and to glucosamine hydrochloride and LMWCS, with cartilage from aged animals showing the greater response. Under stress conditions induced by the proteolytic enzyme pronase and under conditions of mechanical compression, cartilage production increased; addition of glucosamine hydrochloride and LMWCS significantly increased this production. Under stress conditions induced by stromelysin and under heat stress, cartilage synthetic activity decreased; this effect was normalized or reversed by the addition of glucosamine hydrochloride and LMWCS.

Conclusion: The response of chondrocytes in cartilage explants from aged animals to FCHG49 glucosamine hydrochloride and TRH122 LMWCS, as found in Cosequin, under simulated conditions of joint stress was significantly greater than the response to these compounds in young or nonstressed cartilage. These compounds may act as biological response modifiers, improving cartilage's natural response to conditions of joint stress.

based on the research findings about what the oral GAGs do in cartilage. I think we've learned to delay surgery if there is an OCD lesion in the hock, the stifle joint, or maybe even the shoulder, especially in a younger horse, because some of those cartilage defects will heal over time. Then when you are ready to perform surgery, you have a very focal and circumscribed area to treat, thereby limiting the amount of joint damage. We have used injections in the joint to stabilize the cartilage during that maturing period. We have used the oral GAGs as part of the treatment. What we are trying to do is keep the defects from enlarging while we rest the horses.

Before we had oral GAGs or even some of the knowledge about hyaluronic acid, we would just rest some of those horses and some would heal without surgery. So we have to be careful not to say that the positive outcomes are totally from the use of the oral compounds. The GAGs may be helpful, but they may not change the course of the disease.

I don't think the oral GAGs will replace surgery for severe cases. If you've got a severe defect, the horse is going to be lame until surgery removes the problem.

Hanson: We have used oral GAGs as an alternative therapy for some subchondral cysts in yearlings, especially cysts in the fetlock, that can be difficult to access with an arthroscope. We are hoping that glucosamine–chondroitin sulfate will help over the long term for those cysts, to stabilize them enough from a clinical point of view that their signs will be arrested. That has generally been accepted therapy for certain cysts in the medial femoral condyle and the distal metacarpus if surgical intervention is not an option. With rest for 6 months and the glucosamine–chondroitin sulfate therapy, some horses improve to the point where they are not lame anymore. I'm trying to think of what else we can do other than use joint injections to decrease chronic inflammation. We supplement these horses with oral glucosamine–chondroitin sulfate. If we can't intervene surgically or the lesion is not accessible surgically, we hope the oral product will increase the horses' chances of improving.

Boulton: *I believe there is some evidence that NSAIDs actually potentiate cartilage degradation. So from a scientific standpoint, there may be a benefit to using NSAIDs along with oral glucosamine and chondroitin sulfate. Do you use this combination?*

Mountan: Definitely in the beginning if the horse is lame. The combination of oral GAGs and the NSAIDs

reduces the inflammation and makes the horse more comfortable. As the horse's joints seem to be doing better, we reduce the NSAIDs.

Orth: There is some good information indicating that these drugs can have adverse effects on proteoglycan synthesis. The other thing to keep in mind is that decreasing the amount of pain is not solving the existing joint problem. The pain is there as a warning sign of the joint problem.

Boulton: *We know there are negative side effects to long-term NSAID use such as gastric ulcers, right dorsal colitis, and renal papillary necrosis. Has anybody seen any side effects to long-term use of GAGs?*

Orth: Interestingly, GAGs have been used in people in Europe for approximately 30 years. I've done some initial literature searches looking for evidence of adverse effects in humans, and it is almost nonexistent. I'm not saying that there are no adverse effects, but they are very, very minor when you consider the number of people who have been taking GAGs over the past 30 years. A study that measured various bloodwork parameters in horses given Cosequin noted no abnormalities.²

Experience and Research with Glycosaminoglycans

Boulton: *Have you had a specific clinical case in which GAGs were especially warranted and the outcome was positive with their use?*

Mountan: There have been lots of them—since the quality has improved. I started practicing long before we had any of these compounds. The first oral chondroitin products sounded good, but when I tried them I didn't see any benefit. We found out later that the products weren't being absorbed properly and the combination wasn't right. Since we have been using the newer combinations, the horses last a lot longer athletically. They need fewer NSAIDs and fewer joint injections. I have a 29-year-old retired boarder that was a show hunter. He has had a couple of bouts of equine protozoal myeloencephalitis and had numerous other problems last year. I told the owner we should probably put him down. But then I started him on Cosequin in the fall, and now he is unbelievable. He is out in a field with an old hackney pony, and he runs over to the gate, rears up, spins around, and challenges the pony. Cosequin has made a huge difference in a horse I see daily where nothing else has changed.

Boulton: Aside from osteoarthritis, is anybody using oral glucosamine and chondroitin sulfate in any other types of cases?

White: We have used them in horses that have had severe septic arthritis and continue to have a chronic inflammatory response. I have not recommended them for tendon injuries other than for some cases of navicular disease in which I think the tendon is involved. Now that we know tendon lesions are present in navicular disease, I am curious if some of the response from using glucosamine and chondroitin sulfate might have been an antiinflammatory effect.

Boulton: Researchers recently released the results of a study in which they thought they saw increased collagen production in cell cultures of chondrocytes, tenocytes, and ligaments that were incubated with glucosamine and chondroitin sulfate.³

Relevant Research: Effects of Cosequin on Collagen Synthesis in Connective Tissue Cells

Lippiello L, Prudhomme A: Acceleration of collagen synthesis in bovine chondrocytes, tenocytes and ligament cells by exposure to micro levels of glucosamine HCl and chondroitin sulfate. *Osteoarthr Cartil* 12(suppl B):S53, 2004.

Objective: To determine the effects of Cosequin on collagen production in chondrocytes, tenocytes, and ligament cells.

Methods: Collagen synthesis was determined in cultures of these cells exposed to Cosequin versus controls.

Results: Cosequin significantly increased collagen production in chondrocytes, tenocytes, and ligament cells. Very low levels of Cosequin, which are obtainable by the recommended oral dose, induced these increases.

Conclusion: By improving collagen synthesis, Cosequin not only directly supports cartilage matrix production but also helps guard against instability of the joint and thereby further protects the joint structure and function. The noted effects may make supplementation with Cosequin useful after joint injury.

Mountan: We also have a lot of Lyme disease. When I am treating it, I often add GAGs like Cosequin as joint supplements. You have to kill the organism, but helping the joints and muscles is a good idea, too. I actually use it in treating some of the horses that have Lyme disease.

Boulton: Do you use the product in young animals?

Mountan: I do. If there is any kind of joint problem after a septic arthritis or if there is a really crooked foal that is grinding its joints down, I give the foal all the support I can. And, of course, we use the oral product after surgeries—particularly OCD surgeries.

Selecting a Product

Boulton: How do you choose among all the products on the market that contain chondroitin sulfate with glucosamine? Do you look for anything specific in an oral glucosamine-chondroitin sulfate combination?

Mountan: The horse owners in our area are pretty sophisticated. They read all the magazines. They are exposed to many different products, and those products are making different claims all the time. Scientifically, I don't know which claims are accurate. A lot of my clients try different things. I always tell them I think Cosequin is the best. Cosequin has been fairly consistent and seems to work the best. A horse is a tough experimental animal because there are so many variables. I rely on my good owners and trainers and their opinions as to what is really working for their horses, and they tell me Cosequin is very effective.

White: I don't know what to believe. The owners come in with the different compounds they have used, and they tell me a certain one seems to be working. Cosequin is the only one I consistently recommend because work completed by Nutramax confirmed that Cosequin contains the concentrations listed on the package insert.

I do believe that a placebo effect occurs in veterinary medicine. We have to take that into account. Because the owners are paying so much attention and doing a great job taking care of their horses, they are real believers in whatever they are doing. That is fine, except scientifically that belief isn't always dependable when evaluating a treatment.

Boulton: I believe I have read that the human placebo effect can be as great as 30% to 40%.

Hanson: We did a randomized, double-blind, placebo-controlled study on Cosequin.⁴ The owners evaluated the horses daily, and the veterinary investigator evaluated the horses initially and then at 4 and 8 weeks. In scores assigned by the investigator and the owners, the degree of lameness decreased in those horses treated with Cosequin.

Boulton: One report in the literature stated that many of the advertised ingredients on the different bottles of glucosamine and chondroitin sulfate weren't even in the products.⁵ What should we tell the owners about these products?

White: I think we tell them this is not a regulated industry and we mention which compounds have been investigated for false claims. It is our clients' decision.

Mountan: Sometimes you get what you pay for.

Boulton: And sometimes you don't. In that study, the most expensive products on the shelf were some of the ones that were the worst as far as what was actually in the bottle. The advertised contents just weren't there.

Orth: Some areas of concern regarding chondroitin sulfate are its purity, its molecular weight, and the amount in the final product. I tend to look at the products for which the company has actually done some research. Some products just seem to piggyback on others' work.

Boulton: So you shouldn't take one company's data on a specific product and extrapolate that to another product?

Orth: Absolutely not.

Boulton: The ingredients, the formulations, the bioavailability, the purity—they could all be different.

Hanson: But clients use that information. If a specific ingredient worked and one product has it and another product has 10 times that much, they say, "Doc, we want to use this." I say, "Fine. Go ahead and try it, and if it doesn't work, call me back and we'll go back to round one."

Compliance Issues

Boulton: Do you find compliance issues with the oral compounds because of cost?

Hanson: Obviously, some clients can't afford it. Generally, however, if there is a significant enough positive response to a product within the first 30 days, the clients are far more likely to continue with that dosage at least during the competitive season. Then they might drop down to a maintenance dose during the off-season.

Mountan: If cost is a factor, a lot of people want to get back to the maintenance dose as quickly as possible. Unfortunately, that doesn't always work. There is an obvious concern about the dosage of the injectable

joint supplements and the size of the animal. The fact that the dosages for a pony and a big horse are identical doesn't appear to make much sense. At least with the oral compounds, you can attempt to adjust the dosage according to the size of the animal.

Cosequin is the only joint compound I recommend. It contains the concentrations listed on the package insert.

Alternative Treatment Options

Boulton: Horse owners have a variety of compounds at their disposal, even beyond oral glucosamine and chondroitin sulfate. What is your opinion on compounds such as green-lipped mussel (*Perna canaliculus*), yucca, methylsulfonylmethane (MSM), and omega-3 fatty acids?

Hanson: We find that if clients do not want to pursue GAGs, a common response is that they are using a product that contains MSM and they like the effect that it is having. Of all the products out there, MSM is very popular.

Mountan: A significant number of my clients seem to think the MSM does help. We have a lot of horsemen with disposable income. They believe every ad they read and try everything.

White: We get horses that are already on these treatments and still have a problem. If there is any value to these products at all, it certainly is not at the level of disease we are seeing. Again, horse owners will claim

they have used something and it seems to work. With the natural course of some diseases, there is no way to know if these treatments actually work. My thought is that most of those other compounds are not of any value. If the green-lipped mussel really does what it says and you feed the horse enough of it, I assume its results would be similar to those of some of the other products. With omega-3 fatty acids, to date it is all word of mouth. There is no proof. It would be nice to believe that there's a positive result, but just as with these oral GAG products some of the time, I think we are taking the owner's word for the results. Some of the owners are right on target, and some just feel good about it.

Orth: I think the omega-3 fatty acids and other bioactive fatty acids represent an interesting approach because they should be working differently than the glucosamine-chondroitin sulfate. One is maybe working at the extracellular level, and one may be working with different cell signals like nitric oxide. With the omega-3 fatty acid approach, you are changing the substrates for the synthesis of specific inflammatory mediators. It would be intriguing, for example, to compare the functional differences between glucosamine-chondroitin sulfate and diets that have higher levels of omega-3 fatty acids.

Future Research

Boulton: *Are there any directions we should be taking from a research standpoint?*

Orth: The \$64,000 question is "How are these compounds working?" I recognize the problems with the various models that have been mentioned, but hopefully we can identify the mechanisms involved using in vitro studies. Perhaps those studies will help us be able to say, "Look, you give *this*, and it will actually do *this* in an animal—it will reduce the cytokine levels and lower the MMPs." I think that is a big issue, especially for the skeptics out there who continually question how these compounds work. We need to be able to provide definitive answers like those that exist for pharmaceutical

products. For instance, everyone knows what to expect from a COX-2 inhibitor. On the human side, at a rheumatology meeting in England, 50% said they recommended glucosamine and 50% did not. The group that did not recommend glucosamine said it was because no one really knows what its mode of action is. I think that addressing some of those questions could really help.

Boulton: *Do you think we can take the in vitro work and apply it in vivo and feel comfortable that we are doing the right thing for our patients?*

Orth: I think so. If you look at the data from in vitro studies, they make sense when compared with the clinical responses. We are seeing antiinflammatory effects in vitro, and the clinicians are describing the same effects in the horses. The next step is to monitor these changes at the gene or protein level. The other exciting thing is that biochemical assays are available that will allow us to monitor collagen degradation. Collagen degradation is a critical step in the pathogenesis of osteoarthritis, and monitoring it will hopefully provide biochemical data to compare with clinical evaluations.

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