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The Myths of Vegetarianism

Herbal Medicine for IBS

The Corporate Marketing of Soy Foods

Green-Lipped Mussel Effective Against Arthritis

Dr. Klenner's Treatment Protocol for MS

Brassica Vegetables Proven To Cure Cancer

Metabolic Typing for Syndrome X

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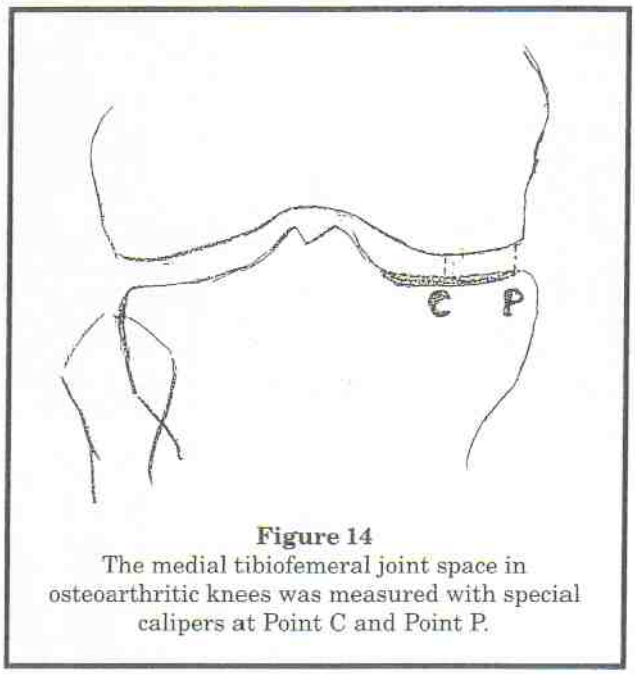
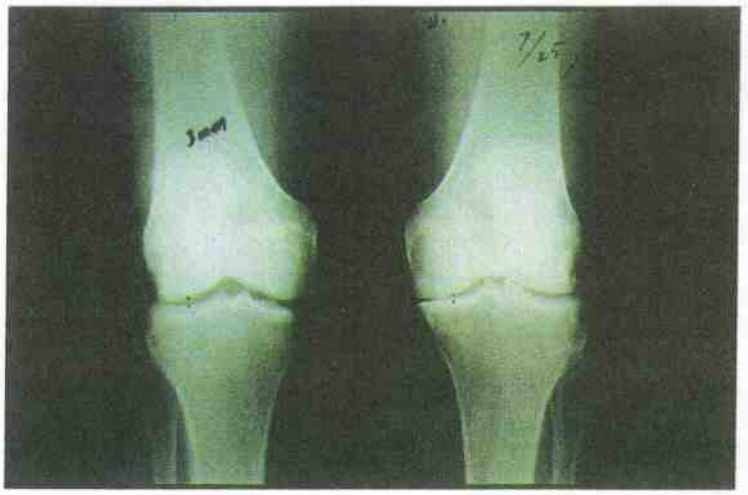


Figure 14
The medial tibiofemeral joint space in osteoarthritic knees was measured with special calipers at Point C and Point P.



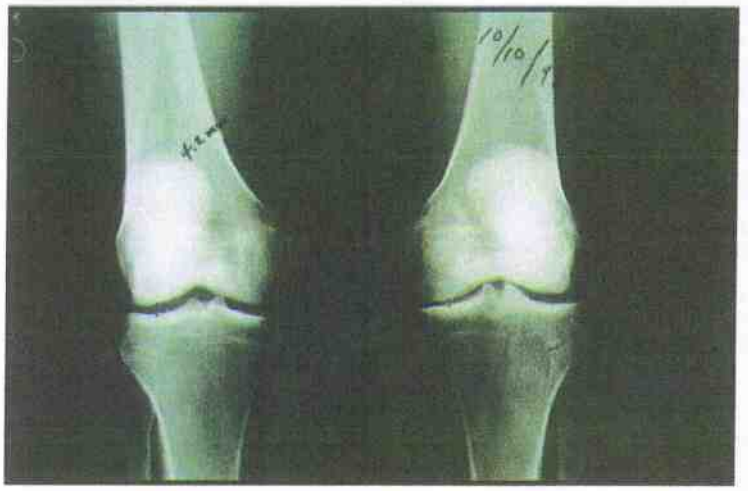
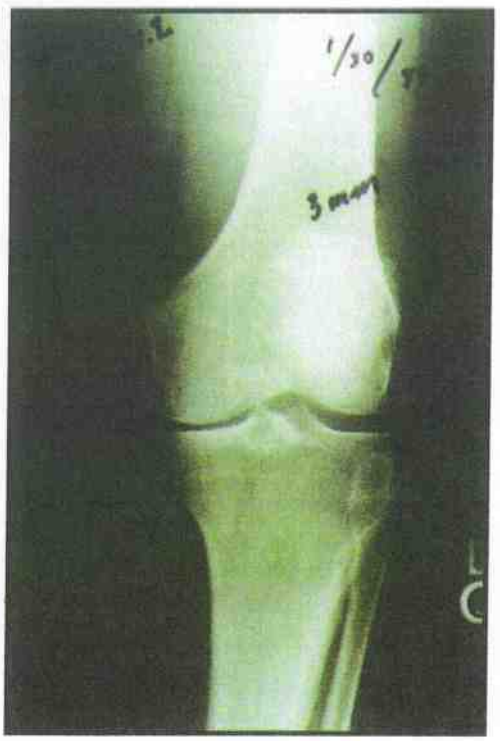


Figure 15
Standing X-rays (A.W.). A 53 year-old male with Grade III osteoarthritis – genu valgus on right and genu varus on left – showing reversal of the progressive joint space narrowing over a period of 15 months.



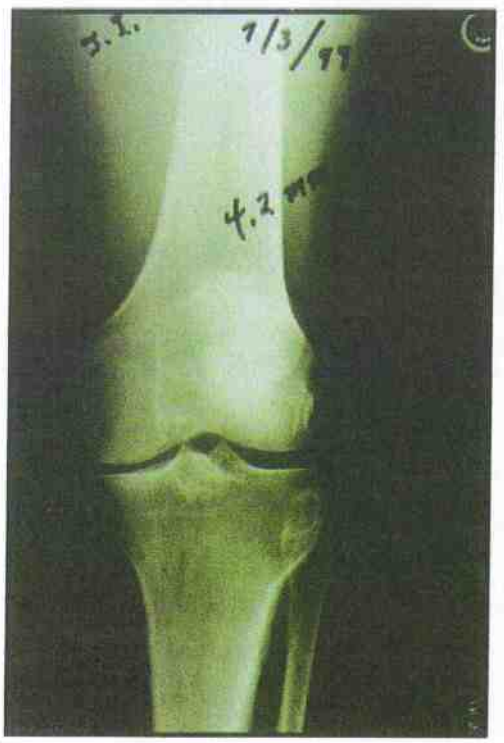


Figure 16
Standing X-rays (D.L.). A 51 year-old female with grade III osteoarthritis genu varus showing reversal of the progressive joint space narrowing over a period of 17 months.

New Research and a Clinical Report on the Use of *Perna Canaliculus* in the Management of Arthritis

by Roger V. Kendall, PhD, Vice President of Research and Development, FoodScience Corporation, John W. Lawson, PhD, Department of Microbiology and Molecular Medicine, Clemson University & Lloyd A. Hurley, MD, Corrales, New Mexico

Abstract

Perna canaliculus (Perna) is a species of green-lipped mussel found off the waters of New Zealand. For centuries this edible shellfish has been a major part of the diet of the local populations. In 1974 it was found to be a potential natural remedy for arthritis.[1] Numerous animal and human studies, published between 1975 and 1993, have indicated that this product from the sea might offer safe and effective relief from the pain, inflammation, and other debilitating symptoms associated with both rheumatoid and osteoarthritis.[2-12] Earlier animal studies focused primarily on the anti-inflammatory properties of Perna mussel and its ability to prevent the onset of induced arthritis. Several human studies gave positive results as to the mussel's ability to relieve multiple symptoms of arthritis when compared to conventional anti-inflammatory drugs.[9,10] The beneficial properties of Perna have been linked to the presence of complex polysaccharides known as glycosaminoglycans (GAGs)[13-15] but studies have also shown that other components in Perna mussel may also contribute to its therapeutic effects. Recent findings at Clemson University confirmed the earlier anti-inflammatory properties of Perna in both rat and mouse arthritic models.[16,17] Perna mussel also exerts a strong immune modulating effect which may explain its mechanism of action.[16-19] A recently completed clinical evaluation on over 100 patients suffering from osteoarthritis of the knee demonstrates Perna's potential in providing effective management of arthritis. *Perna canaliculus* has been shown to relieve arthritic symptoms and may halt the progression of the condition as well as provide nutritional support for the actual regeneration of connective tissue in the affected joints.

Introduction

Perna canaliculus, also referred to as the green-lipped mussel, has been commercially available as a food supplement in the United States since 1975. Perna is a natural product from the sea that has an exceptional ability to aid the body in halting the progression of joint and connective tissue disease as well as promote the regeneration and healing of arthritic and injured joints. The product contains natural anti-inflammatory agents, immune modulators and many essential building blocks needed to rebuild collagen, proteoglycans and synovial fluid found in the joints, ligaments and tendons. Perna can significantly reduce the pain, swelling and inflammation associated with connective tissue and musculoskeletal problems and improve joint mobility and exercise tolerance.

Perna is a pure, nutritional, whole-food product that possesses an exceptional degree of biological activity. As a product of marine aquaculture, *Perna canaliculus* is grown commercially in the pure, pristine waters off the coast of New Zealand. It has been a valuable food source for the native people of New Zealand for centuries. This edible green-lipped shellfish contains the ocean's natural mineral balance which is similar to that found in the human body. Perna mussel is harvested at the peak of its growth curve. The soft tissue is separated from the shell, flash frozen, lyophilized (freeze-dried to remove the water) and processed into a fine powder. The manner in which Perna is concentrated does not destroy or inactivate the biologically active constituents. Perna contains proteins, complex carbohydrates, lipids, naturally chelated minerals, nucleic acids and mucopoly-saccharides (glycosaminoglycans) that provide nutritional support to the body and especially to the joints. The protein efficiency ratio (PER) for Perna is 3.6, showing that it is a high quality protein product.[20]

Composition of *Perna canaliculus*

	Percentage Range
Protein (amino acids)	60-62%
Carbohydrates	12-14%
Glycosaminoglycans (chondroitin sulfates)	11-12%
Lipids	4-5%
Minerals	4-6%
Water	3-4%

During the 1960s researchers working in Britain and the United States began a comprehensive search of marine organisms in an attempt to isolate possible natural drugs for the treatment of cancer. A large number of shellfish products were investigated, including the green-lipped mussel *(Perna canaliculus). Perna canaliculus* was tested in a group of human cancer patients without discernable results. What was interesting about this study was that patients who were coincidently suffering from arthritis reported less pain and joint stiffness along with improved mobility. These results prompted further research into its possible value against degenerative joint and connective tissue disorders. A number of reports with human arthritic patients in the 1970s and 1980s gave mixed results as to its value. However, later studies found that Perna mussel does contain a number of biologically active constituents, which could both prevent and reverse inflammatory joint disorders. Two human clinical studies on Perna mussel showed positive results against osteo and rheumatoid arthritis.

Perna mussel has been used successfully to treat degenerative joint disorders and arthritis in both human and veterinary health fields. Perna has been found beneficial in reducing pain, stiffness and inflammation in the afflicted areas as well as increasing joint mobility. Positive reports on the use of Perna from doctors and patients have been reported for over two decades. Lloyd Hurley, MD, of Corrales, New Mexico has reported that several of his

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patients avoided knee surgery since Perna was added to their therapeutic program to treat their osteoarthritis. After nine to twelve months on the product, radiographic evidence has confirmed that cartilage had begun to regenerate in the afflicted joints of several of his patients. Results show that Perna represents a significant and beneficial treatment program for both rheumatoid and osteoarthritis. Anecdotal reports from many practicing veterinarians have confirmed clinical efficacy in treating degenerative joint disease in both dogs and horses.

Arthritic and Musculoskeletal Disorders

Joint and connective tissue problems associated with many forms of arthritis rank as the number one disability disease in the United States. Over 40 million people have severe health problems due to many different forms of arthritis, the major forms being osteoarthritis and rheumatoid arthritis. Other forms include gout, ankylosing spondylitis (AS) and infectious arthritis. Factors that contribute to arthritis include: wear and tear on joints (excessive stress); injuries; infections; genetic factors; drug side effects; nutritional deficiencies; hormonal factors; age-related changes; altered immune system; biomechanical factors; excessive weight.

Arthritis is generally an inflammatory disease characterized by swelling, stiffness and/or pain in the joints. All joints of the body can be affected. Chronic forms of the disease may be associated with deformity and restricted range of motion. The exact cause and progression of many forms of arthritis are not well understood.

Osteoarthritis: Over 30 million Americans have this form of arthritis, which may be accompanied by inflammation. This degenerative joint disease is related to a wear and tear phenomenon. Over time, the smooth surface of cartilage that covers the ends of the joint bones can become rough. This process can lead to a gradual breakdown of the connective tissue surrounding the joint. Injury to a joint can also create a progressive deterioration of the cartilage. In either situation, friction in the joint can lead to inflammation and weakened tendons, ligaments and muscles that surround the joint, causing the development of small bony growths, calcium spurs and soft cysts in the joints.

Osteoarthritis is characterized by joint pain, inflammation of the synovial membrane and loss of joint cartilage as a result of the increased breakdown of the proteoglycans in the cartilage matrix. As the disease progresses, synovitis and joint enlargement occur leading to a decrease in joint motion and the release of destructive enzymes, called lysosomes, which break down cartilage.[21] Release of free-radical mediators also contributes to major cartilage degradation.[22] The severity of the disease appears to correlate with the loss of glycosaminoglycan (GAG) content within the joint and surrounding articular cartilage.[15] Glycosaminoglycans are a major component of cartilage and connective tissue.[14] Cartilage production can also slow down significantly and even stop entirely as a result of the disease.

Rheumatoid Arthritis: This form of arthritis affects more than 3 million people. It is an example of an autoimmune disease where the body's immune system attacks its own joints. This form of arthritis is a systemic, inflammatory disease that attacks the synovial membranes surrounding the lubricating fluid in the joint. The cartilage, along with the bone structure, is slowly destroyed leading to scar tissue formation. In the extreme form of the disease, the joint may actually fuse. This condition, which can affect any joint in the body, can lead to fatigue, weight loss, joint stiffness and debilitating pain. This form of arthritis can lead to major deformity and loss of motion over time.

Infectious Arthritis: There is good evidence that some forms of arthritis can be caused by parasites, viruses, fungi and bacteria. One such example of Infectious Arthritis would be Lyme Disease. Bacteria, which are transmitted by deer ticks, can invade the bloodstream and travel to the joints resulting in arthritis-like symptoms after 30 to 40 days. In many ways, Lyme Disease resembles rheumatoid arthritis.

Ankylosing Spondylitis (AS): This arthritic disease affects the joints of the trunk, including the spine and the pelvis. As it develops, AS can lead to extreme low back pain that persists for many months. Over time, the spine gradually becomes stiffer. Other symptoms include the inability to expand the chest, severe pain and eye inflammation.

Cartilage and Joint Metabolism

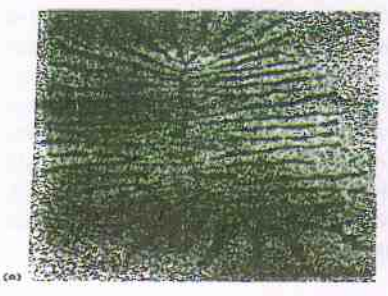
Before discussing the role of *Perna canaliculus* in helping to improve arthritis, it may be useful to present a short description of articular cartilage, the major connective tissue capping the ends of bones around the joint. Cartilage provides smooth surfaces for unrestricted joint movement and acts as the principle shock absorber during times of stress on the joint.

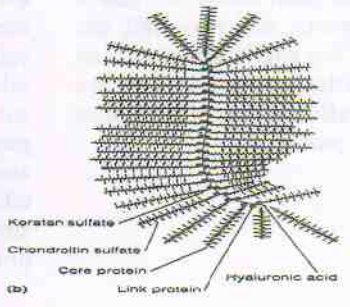
Cartilage is made up of 4 major components: collagen (protein); proteoglycans (complex of protein and glycosaminoglycans); water; and chondrocytes (cells). As with all components of the body, cartilage is continually broken down and rebuilt in response to the stress placed on the joint. Enzymes secreted by the chondrocytes work to degrade collagen, which is then rebuilt. Proper collagen turnover,

Figure 1 – Proteoglycan Structure

Credit: *Biochemistry*, 2nd Ed. C.K. Mathews and K.E. Van Holde ©1996. Reprinted by permission of Addison Wesley Educational Publications, Inc.

Proteoglycan structure in bovine cartilage. (a) An electron micrograph of a proteoglycan aggregate. (b) A schematic drawing of the same structure. Keratan sulfate and chondroitin sulfate are covalently linked to extended core protein molecules. The core proteins are noncovalently attached to a long hyaluronic acid molecule with the aid of a link protein.





(a) Courtesy of J.A. Buckwalter and L. Rosenberg from *Collagen Relat. Res.* (1983) 3:489-504, Amsterdam: North Holland, 1975.

including adequate synthesis, is key to proper joint health and function.

The proteogylcans are made up of a protein core and several complex amino sugars known as glycosaminoglycans (GAGs). Three principle GAGs found in joints are hyaluronic acid (also found in the synovial fluid), keratin sulfate and chondroitin sulfates (see Figure 1). The principle function of GAGs is to increase lubrication of the joint and provide shock-absorption via incorporation of water molecules into the matrix. Both are essential for proper joint function. GAGs, synthesized by the chondrocytes, require a steady supply of glucosamine and other building blocks including a source of sulfate groups. Synthesis of GAGs is the limiting factor in cartilage generation.[22]

There are three factors that should be noted in maintaining proper joint function and reversing arthritic damage. First, adequate raw materials need to be supplied to the chondrocytes to rebuild cartilage. Second, there must be a shift in chondrocyte activity from collagen degradation to a greater repair and rebuilding mode. At the same time, production of the proteolytic enzymes that cause cartilage degradation must be reduced and inflammation must be brought under control. It is now believed that protein structures known as cytokines, produced from various immune cells, control the inflammation process. Their regulation may be the key to enhancing joint repair and regeneration. Perna contributes chondroitin sulfates and other building blocks for GAG synthesis and decreases the inflammation process by down-regulating the pro-inflammatory cytokines. Both aspects help to decrease loss of cartilage and increase joint repair.

An effective approach to reversing the destruction of arthritis should provide support by:

- Decreasing inflammatory response and pain
- Enhancing cartilage synthesis by the chondrocytes
- Reducing the destruction of cartilage caused by degrading enzymes and free radicals
- Modulating the immune responses to reduce autoimmune response and pro-inflammatory cytokines

Natural components within the Perna mussel potentially support joint health in all of these areas as discussed below.

Glycosaminoglycans (GAGs)

Perna canaliculus provides a rich source of glycosaminoglycans (approximately 12% GAGs), which are principle components of cartilage and the synovial fluid found in the joint. GAGs are synthesized by the chondrocytes and other local tissues and are essential in stabilizing the joint and providing shock-absorption. GAGs are complex amino sugars that may contain phosphate or sulfate groups that increase the uptake of water into the cartilage matrix. This "hydration" of joints, which decreases with age, is critical to the lubrication and shock absorption property of joints. A loss of GAGs leads to greater stiffness in the joint and increased potential for injury.

There are nine principle classes of glycosaminoglycans (GAGs), which are long, unbranched chains made up of complex sugars (disaccharide repeating units). Five GAGs that have relevance to connective tissue are:

- Chondroitin-4-sulfate
- Chondroitin-6-sulfate
- Keratin sulfate
- Dermatan sulfate
- Hyaluronic acid

Chondroitin-4-Sulfate and Chondroitin-6-Sulfate make up the basic ground substance of both bone and cartilage. Hyaluronic Acid is a non-sulfated GAG found in the proteoglycan structure and it also contributes to the viscosity of the synovial fluid. In addition to lubrication of the synovial membranes, GAGs provide flexibility, elasticity and tensile strength to the articular cartilage. The severity of arthritis is directly related to the loss of GAG content within the joint and surrounding cartilage.[13-15]

As a source of GAGs, Perna can provide the chondrocytes with chondroitin sulfates and other precursors needed to improve the viscosity of the synovial fluid and enhance synthesis of the proteoglycans in the articular cartilage. Such support is critical for reversing the arthritic process. GAGs can also exert a strong anti-inflammatory action on connective tissue. Evidence suggests that they effectively inhibit the action of degrading enzymes, which contribute to cartilage breakdown.[21,22]

Perna canaliculus

How Does Perna Work to Improve Joint Function?

The exact mechanism or mechanisms, by which *Perna canaliculus* works to control and perhaps reverse arthritis is not yet clearly understood. Research over the past 20 years has revealed that Perna contains a number of potentially active compounds that work against inflammation and the destructive cycle of degenerative joint disease.[7,11,12,23-25] The unique combination of biologically active compounds, chelated minerals, glycosaminoglycans (chondroitin sulfates), amino acids, nucleic acids and essential fatty acids may yield a synergistic effect that promotes repair of the articular cartilage and reduces further deterioration of the joint.

Clinical evaluation reveals that the components in Perna mussel improve joint lubrication, reduce inflammation and joint pain and improve the mobility and range of motion of the affected joint. As a nutritional supplement, Perna provides some of the key building blocks that the body uses to rebuild cartilage and may even work to deactivate the cartilage-destroying enzymes that cause further deterioration. Perna appears to work directly on chondrocytes (cells that are involved in manufacturing cartilage) to repair damaged cartilage and improve connective tissue elasticity.

Recent work at Clemson University, conducted by John Lawson, PhD, has found that immune response changes in both osteoarthritis (degenerative joint disease) and rheumatoid arthritis may be important indicators in the progression of the disease.[26-29] Lawson has discovered that *Perna canaliculus* does have immune modulating properties that may actually down-regulate the pro-inflammatory cascade in arthritis. Last of all, Perna may have an effect on reducing cell apoptosis, a mechanism that eliminates aberrant immune cells that may prompt joint degeneration and inflammation.[16] This finding, correlated with a decrease in inflammation, suggests that there may be a decrease in the generation of pathological immune cells, which the host then attempts to eradicate by apoptosis.

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Potential factors that may explain the beneficial effects of *Perna canaliculus* in reversing arthritis include the fact that it:

- Provides the necessary building blocks to rebuild damaged cartilage in the form of amino acids, chelated minerals, glucosamine and glycosaminoglycans (GAGs).
- Exerts an anti-inflammatory/ analgesic effect.
- Contains chondroitin sulfates that may inhibit enzymatic breakdown of the cartilage and connective tissue.
- Causes an immune response shift which helps down-regulate the inflammatory cytokines.
- Causes reduction in apoptosis response that may indicate a decrease of wayward cells contributing to the destructive cycles of arthritis.
- Contains an anti-histamine factor and prostaglandin inhibitors that reduce inflammation.
- Provides extremely valuable Omega-3 eicosatetraenoic acids (ETAs), which are potent inhibitors of the cyclooxygenase and lipoxygenase pathways in which leukotrienes and other inflammatory agents are produced.

Research on the Anti-inflammatory Effect of Perna canaliculus

Cullen and co-workers first published a report on the anti-inflammatory properties of the Perna mussel in 1975.[2] In 1980, an article by Ramsford and Whitehouse published in the *Journal of Arzeim-Forsch* entitled "Gastroprotective and Anti-inflammatory Properties of Green-Lipped Mussel *(Perna Canaliculus)* Preparation," reported modest anti-inflammatory activity in an induced arthritis model in rats.[11] The product also showed reduced gastric ulerogenicity caused by several NSAIDs (non-steroidal anti-inflammatory drugs). Three articles published in the *New Zealand Medical Journal* by Miller et al. (1980, 1981, and 1984) reported that the anti-inflammatory activity of the Perna mussel in rats was associated with a protein fraction.[4,6,23]

An article entitled "Anti-inflammatory activity of glycogen extracted from *Perna Canaliculus* (NZ Green-Lipped Mussel)" by Miller and Dodd published in *Agents Actions* (1993), reported that an aqueous fraction containing a high molecular weight material, possibly a polysaccharide (glycogen), inhibited experimentally-induced inflammation in rats when administered by injection.[12] This suggests that the anti-inflammatory activity resided with the glycogen fraction.

A lipid fraction isolated from *Perna canaliculus* by extraction has also shown anti-inflammatory properties.[25,26] An article published in *Inflamopharmacology* (1997) by Whitehouse et al, entitled "Anti-Inflammatory Activity of a Lipid Fraction from the NZ Green-Lipped Mussel," reported dose correlated anti-inflammatory activity from a lipid extract of the mussel given to rats with adjuvant induced polyarthritis. The anti-inflammatory response was linked to certain polyunsaturated fatty acids that were isolated from the New Zealand green-lipped mussel.

Kosuge et al, (1986) successfully isolated an anti-histaminic compound called Lysolecithin from green-lipped mussel.[24] Lysolecithin was found to have anti-inflammatory activity in an induced arthritic model in rats. In another study, Perna was also shown to decrease prostaglandin synthesis, another major factor in the inflammation process.[23]

These reports seem to indicate that there are multiple anti-inflammatory agents present in Perna which include glycogen structures, glycosaminoglycans (GAGs) and certain lipid fractions. Overall, this may indicate that the whole mussel organism can contribute to a better anti-inflammatory response than by using a fractionated extract that would contain only one of the active factors.

Research at Clemson University

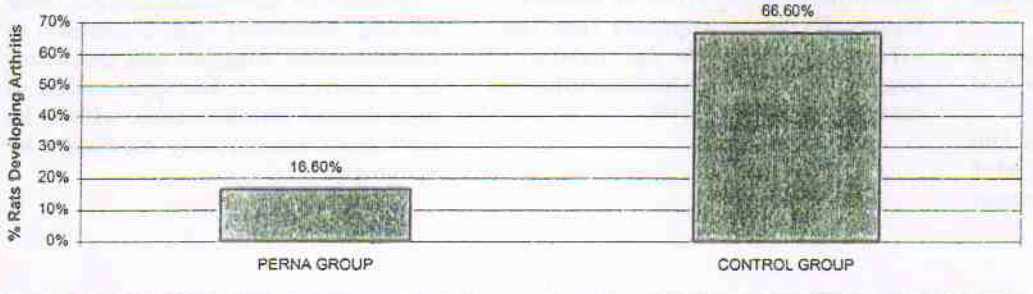
John Lawson, PhD, and his research group at Clemson University have completed a number of arthritic studies with Perna in both animal models and in cell cultures, with a special interest in evaluating immune regulation.[28-30] In separate studies using both rats and mice, Perna was shown to effectively reduce the onset of rheumatoid arthritis and to reverse it as well.[16,17]

In a study using outbred rats, both control and test animals were injected with collagen II (C-II) to induce arthritis.[27,32] The test animals were fed Perna (100mg/kg of body weight per day). Incidence of arthritis, the timing and severity of arthritis and IgG and IgM antibody levels to collagen II, in both groups, were analyzed. Only three of the eighteen test animals (16.6%) that were fed Perna developed arthritis, while in the control group, 10 out of 15 animals (66.6%) developed severe arthritic inflammation (Figure 2).[17]

The Clemson results are consistent with previous published reports that Perna mussel produces an anti-inflammatory response. The rats which were on Perna prior to C-II induction of arthritis had a delayed onset of arthritis (one day later) as compared to arthritic controls. Based on joint measurement (average paw size for control arthritic joints was 19.5 mm as compared to 14.2 mm in the Perna group), the arthritis was also shown to be more severe in the control animals as compared to the animals in the Perna fed group that developed arthritis. There was no significant difference in the IgG and IgM antibody response between the Perna treated animals and the control group.

Perna was also effective in decreasing inflammation of

Figure 2 – Clemson University Rat Study



arthritic lesions in mice in which arthritis was induced by the C-II method. In this study mice were randomly assigned to two treatment groups after the development of arthritic symptoms. The first group received standard mouse chow mixed with Perna daily, while the second group received no Perna supplement and therefore served as a control. The Perna fed mice were give 1.2 g Perna per day during the course of the study. Mice were scored in a range from 0 – 3 as a measurement of joint inflammation over a 107-day period. Both groups began the study with the same average score of 2.1 (Figure 3). The endpoint scores at day 107 were averaged and presented in Table 1. The control animals ended the study with an average score of 2.65. The majority of the mice in this group were averaging a daily inflammation score of between 2.5 to 3.0. These mice exhibited severe swelling and edema in all four limbs. In contrast, those animals receiving Perna had an average score of 1.42. These animals displayed minimal inflammation, usually confined to only one limb. Surprisingly a few of the animals in the Perna-fed group displayed no apparent arthritic symptoms at the end of the study.[16]

Table 1: End-point severity inflammation scores in arthritic mice after 107 days

Treatment	Score	Percent
Control	0	0%
Control	1	13.3%
Control	2	26.7%
Control	3	60%
Perna	0	7.1%
Perna	1	57.1%
Perna	2	28.6%
Perna	3	7.1%

Joint Inflammation Scores
(0 = No Inflammation
3 = Severe Inflammation)

The rat and mouse studies point out that Perna mussel may be effective in preventing arthritis as well as reversing the condition. Perna mussel also caused a decrease in apoptosis, or programmed cell death, in lymphocytes obtained from arthritic animals. Control arthritic mice exhibited an elevated background level of constant apoptosis of approximately 25.6% above levels seen in nonarthritic controls. In Perna-fed animals, apoptosis fell significantly by an average of 6.3%. In preliminary studies in humans, we have shown the presence of aberrant apoptosis in both osteoarthritis and rheumatoid arthritis similar to that observed in arthritic mice. Future studies will seek to determine if Perna modulates levels of apoptosis in humans suffering from arthritis.[31]

Cell culture results show that Perna also acts as an immunomodulating agent, affecting both humoral and cellular immunity.[18,19] A Tween-20 extract of Perna with immunomodulating activity was prepared. The activity was measured by bioassays in which supernatants of Perna-treated and untreated immune cells were added to responder cells sensitive to an individual cytokine. Proliferation (increase) or inhibition (decrease) of these responder cells signaled the extent of cytokine production. THP-1 cells, which produced tumor necrosis factor- alpha (TNF-α) with lipopolysaccharide complex (LPS), were treated with Perna for 24 hours. The supernatants were added to L-929 fibroblast cell lines, whose growth is inhibited in the presence of TNF-α. Perna decreased the levels of TNF-α produced by about 50% compared to untreated controls. Similarly Perna lowered the levels of interleukin-1 (IL-1) production in U-937 cell lines, interleukin-2 (IL-2) in both Jurkat E6-1 and EL-4 cell lines and interleukin-6 (IL-6) in LS174T cell lines (Figures 4-9). In addition, the above extract of Perna inhibited the production of antibody in several B cell hybridoma cell lines. As shown by these figures, as the concentration of an inflammatory cytokine decreases concomitant with increases in added Perna concentrations, the viability of the responder cell lines either increase or decrease dependant on their specific response to the individual cytokine. All

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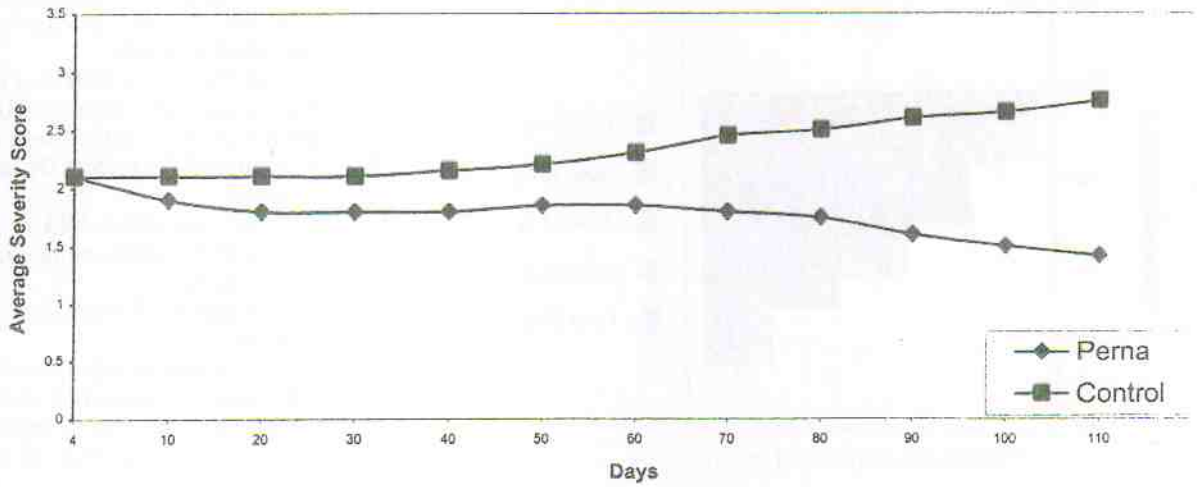
Figure 3 – Arthritic Inflammation in Collagen-Induced DBA/1J Mice
Average Severity Score of Treated (Perna) and Untreated Mice as Recorded Every 10 Days



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immunomodulatory activity of Perna mussel extract could be removed with proteolytic enzymes (Figure 9).

More research is needed to determine whether this decrease corresponds to the down-regulation of inflammatory cytokines (IL-1, IL-2, IL-6, Tumor Necrosis Factor-alpha) and a decrease of aberrant immune cells (apoptosis) that are contributing to the disease. A human study is now planned which will help to answer this question.

A recent study in mice with systemic lupus erythematosis (SLE) has shown that a combination of Perna mussel and N N-Dimethylglycine (DMG) was effective in helping reverse several clinical markers for the disease (see *Townsend Letter*, May 2000). These include significant decreases in the levels of several inflammatory cytokines (including IL-6 and TNF-alpha) and in antinuclear antibodies to both single and double stranded DNA.[33] Preliminary results look very encouraging and more studies in this area are planned.

Earlier Clinical Studies Incorporating *Perna Canaliculus*

Two clinical studies have been previously published using the Perna mussel.

1. Glasgow Homeopathic Hospital Study (1980)

A clinical evaluation of Perna mussel extract was reported in *The Practitioner* (1980) by a team of physicians headed by Robin Gibson, MD.[9] In a preliminary test carried out with 86 patients, 55 had rheumatoid arthritis and 31 had osteoarthritis. The results showed 67% of the rheumatoid and 35% of the osteoarthritic patients showed reduction of symptoms from Perna supplementation. Thirty-eight percent of the 86 patients showed no improvement. This was followed by a double-blind, placebo-controlled study involving an additional 66 patients. Of these, 28 had rheumatoid and 38 had clinical and radiological evidence of osteoarthritis. All patients were taking some form of a non-steroidal anti-inflammatory treatment. Clinical assessments (joint mobility, function tests, swelling, pain index) and laboratory indices were monitored before and after a three month trial period where the test group received 1,050 mg of Perna mussel extract per day and the control group received a placebo.

Results of the study, after removing eight patients who dropped out due to unrelated reasons, were as follows: 76% of the rheumatoid and 45% of the osteoarthritic group reported improvement in the form of reduced pain/stiffness. A total of 23 out of 58 (40%) in the study showed no improvement. Grip strength did not significantly improve in the treatment group. Side-effects were minimal, apart from initial exacerbation of symptoms experienced by six of the 66 patients in the trial from two to four weeks after starting the study. This increased sensitivity lasted from one to two weeks after which time the individuals generally reported improvement in their symptoms. Dosage of Perna extract was dropped to 750 mg per day once a positive response was seen.

Comment on the study: First, the patients in the study had their condition on average for over 15 years (advanced stage). Most were listed as potential candidates for surgery. Stopping the arthritis process and reversing it at this stage is an extremely difficult challenge. Second, a higher dose of Perna mussel may have given enhanced results. Lastly, three months is not long enough to establish clinical evidence for long-term benefit and regeneration of the deteriorated joints. A longer study of up to a year at a higher dosage (from 1-3 grams of Perna per day) using less advanced arthritic patients may have shown greater effectiveness of the Perna preparation.

2. French Study Involving Osteoarthritis of the Knee (1986)

In a study completed at a Paris hospital and published in the *Gazette Medicale* (1986), Audeval and Bouchacourt reported on results of a placebo-controlled, double-blind study using a mussel extract of *Perna canaliculus* in 53 patients suffering from osteoarthritis in the knee.[10] To qualify for the study, the patients' conditions were confirmed by radiographic analysis and all had clinically experienced a steady pain for several weeks. The study lasted 6 months using 6 capsules (2100 mg Perna extract per day) versus a matched placebo. Ten efficacy measures were employed and patients were examined monthly.

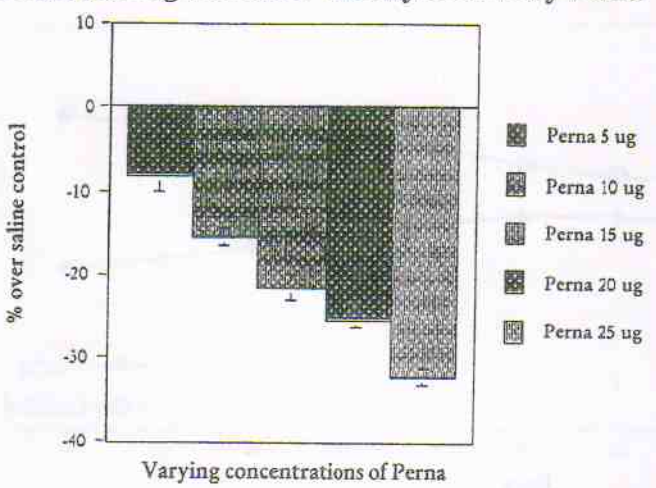
Results showed that the Perna group was statistically superior to the placebo group in 4 of the 10 test areas:

- Pain and discomfort (Husrisson's scale)
- Functional index ARA
- Patient's opinion on results of treatment
- Treatment effectiveness judged by doctor

The placebo group showed a greater reduction in "morning stiffness" as compared to the Perna extract group. The severity of the illness also

Figure 4

Dose response effects of Perna (Tween-20 extract) on IgG production levels of V2#9 hybridoma. Each data point represents a mean of three independent experiments with triplicate wells.



influenced the results. Perna mussel appeared to be more effective in less serious or moderate cases and not as effective in the more advanced stages. The effectiveness of the product became more obvious towards the end of the six month study. The researchers concluded that *Perna canaliculus* was effective by influencing the evolution of the arthritic illness (stopping the deterioration and enhancing the repair mechanism) rather than by just working as an analgesic or purely symptomatic anti-inflammatory agent.

Comment on the study: The Perna extract was well tolerated by the participants with no adverse conditions reported. The placebo group may have used higher doses of NSAIDs, which would explain less morning stiffness in this group (not documented). No radiographic data was reported after six months, which may have demonstrated possible cartilage rebuilding in the Perna mussel test group. Overall, the study reported that the use of *Perna canaliculus* was beneficial in the treatment of osteoarthritis.

Clinical Experience with *Perna Canaliculus*

by Lloyd A. Hurley, MD

As an orthopedic surgeon I have utilized *Perna canaliculus* for over ten years in my practice as a means of offering my patients nutritional support for their degenerating osteoarthritic knee conditions. For many of my patients, inclusion of Perna, along with other modifications, has allowed them reasonable control of their arthritic condition without resorting to surgery (total knee replacement) as a last resort.

In the search for an even more effective and safe anti-inflammatory agent, the benefits of New Zealand Green-Lipped Mussel *(Perna canaliculus)* seemed promising. Reports in foreign medical and American veterinary literature indicated that the lyophilized powder from the edible portion of this shellfish had remarkable anti-inflammatory as well as chondroprotective and gastroprotective properties.[4,5,9,11,12] An antihistamine property was also reported.[24] John Croft's book hinted that unexplored remedies for human suffering would be found in the sea.[1] This claim was particularly intriguing and encouraging. The remarkable anti-inflammatory properties of the green-lipped mussel were first described by Cullen, Flint and Leider[2] and the first Perna mussel product was distributed for general public use in New Zealand in 1974.

Beneficial response to Perna in my patients suffering from a wide range of orthopedic problems prompted a more detailed evaluation of the effect of this product in the management of gonarthrosis (arthritis of the knee). This was a limited clinical evaluation that lasted over a four year period and did not employ the use of a control group.

Gonarthrosis A Pilot Study

Patients and methods

One hundred and twenty (120) referred patients suffering from radiographically confirmed arthritis of the knee and showing clinical symptomatology of pain were included

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Figure 5

Dose response effects of Perna (Tween-20 extract) on TNF-alpha production of LPS stimulated THP-1 cells. Each data point represents a mean of three independent experiments with triplicate wells.

Decrease in TNF-alpha secretion by THP-1 cells upon treatment with Perna as observed in the L-929 bioassay

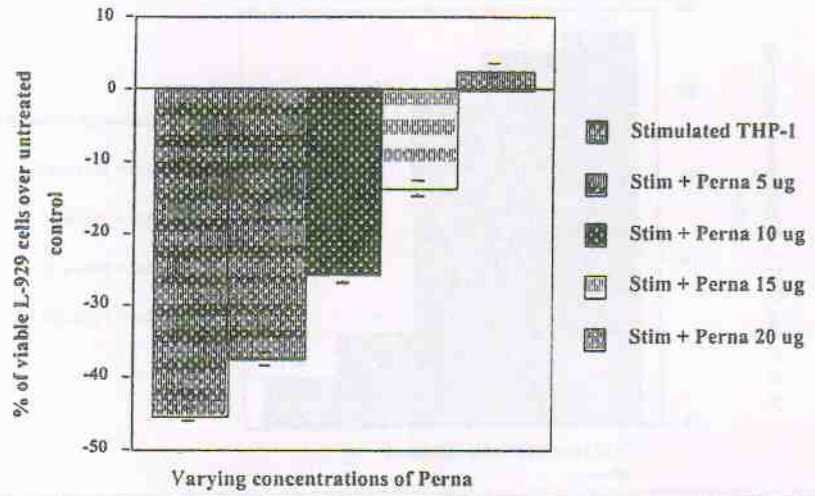
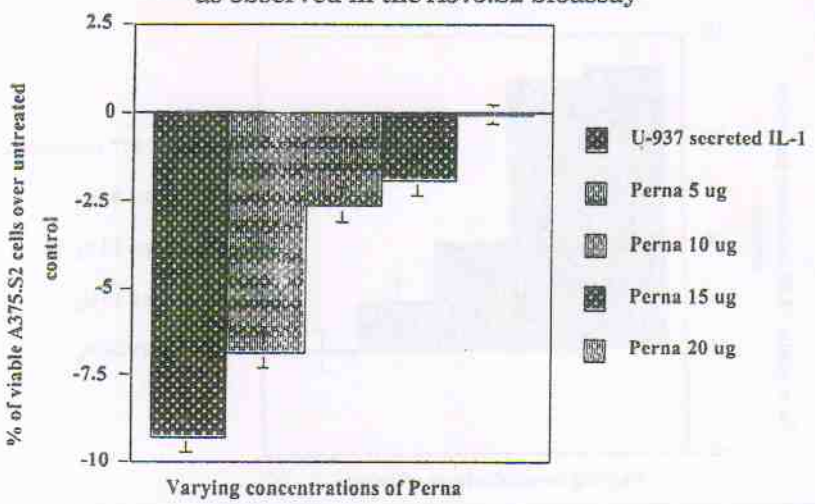


Figure 6

Dose response effects of Perna (Tween-20 extract) on IL-1 secretion of U-937 cells. Each data point represents a mean of three independent experiments with triplicate wells.

Decrease in IL-1 secretion by U-937 cells upon treatment with Perna as observed in the A375.S2 bioassay



in this study. Sixty-four males and fifty-six females made up this group. Ages ranged from thirty-seven to ninety-one. Most of the patients were in their sixties and seventies. Age distribution by decades is shown in Figure 10.

Seventy-nine patients were genu varus (bowlegged), thirty-nine were genu valgus (knock kneed). Two patients were mixed, having both. Several were referred for total knee replacement. One of the patients was referred by his cardiologist suggesting that an experienced doctor in arthritic management should be consulted prior to considering total joint replacement since, from his perspective, the patient was not a safe candidate for surgery.

All patients in the study were provided information on the use of Perna mussel for degenerative joint disease.

Figure 7

Dose response effects of Perna (Tween-20 extract) on IL-2 production of stimulated Jurkat E6-1 cells.Each data point represents a mean of three independent experiments with triplicate wells.

Decrease in IL-2 secretion by stimulated Jurak E6-1 cells upon treatment with Perna as observed in the CTLL-2 bioassay

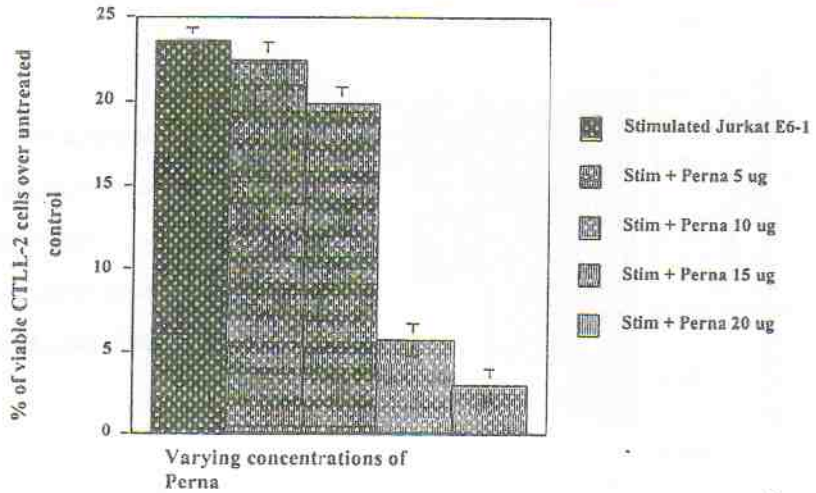
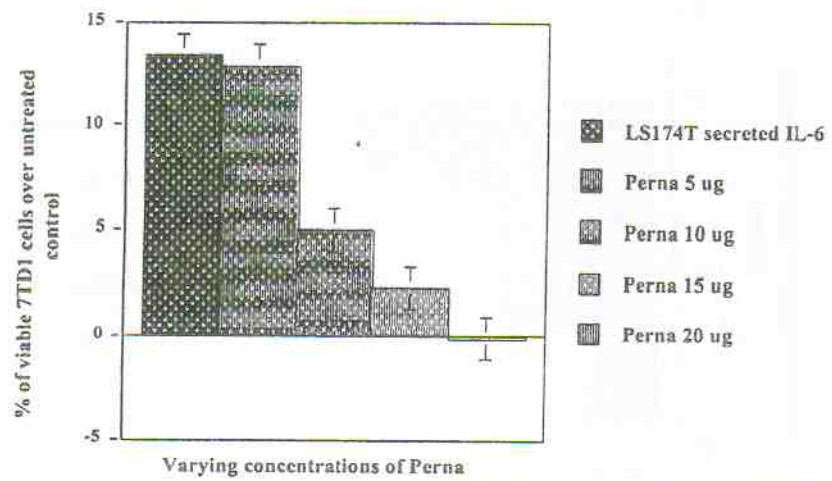


Figure 8

Dose response effects of Perna (Tween-20 extract) on IL-6 production of LS174T cells. Each data point represents a mean of three independent experiments with triplicate wells.

Decrease in IL-6 secretion by LS174T cells upon treatment with Perna as observed in the 7TD1 bioassay



They were advised that Perna had been shown to have an anti-inflammatory effect equal to that of Indocin,[3] but more significantly it had a nutritive metabolic effect.[4] The importance of mucopolysaccharides (glycosaminoglycans) in the formation of basic proteoglycan cartilage was stressed. The patients were shown illustrations indicating the architecture of a cartilage proteoglycan showing how chondroitin sulfate, keratin sulfate and hyaluronic acid combine with a link protein to make a cartilage proteoglycan model.[15] (See Figure 1) They were encouraged to read the popular book *The Arthritis Cure* by Jason Theodosakis, MD, to reinforce the message that certain oral chondroprotective products were finding acceptance as part of the treatment of arthritis.[21]

Patients with a known allergy to seafood, shellfish or alfalfa were excluded from this study. Patients who were taking some form of nonsteroidal anti-inflammatory or pain medication were allowed to continue but were requested to keep a record of all medications required.

Pain Assessment

The Huskinson visual analogue pain scale was used by the patient to assess pain.[34] The pain intensity ranges from "no pain to worst possible pain" on a scale of 1 to 10 (See Figure 11). Pain scores were monitored throughout the study. If pain was expressed as above 5 on the visual analogue scale an initial injection of Triamcinolone 40 mg, Dexamethasone 6 mg, and Marcaine .05% 3 cc, was given intra-articularly.

Biomechanical Adjustment

Patients with genu varus (bow leg) were referred to a local shoemaker for 1/8" outer heel wedges and 1/8" outer sole wedges. Patients with genu valgus (knock knee) were referred for 1/8" inner heel wedges and 1/8" inner sole wedges

Inflammatory Index

An estimate of overall inflammatory activity of the joints based upon clinical evidence of swelling, trauma, redness, pain and heat was made. This differs very little from Hippocrates' "Dolor (pain), Rubor (redness), Color (heat) and Tumor (swelling)." A history of "minutes of morning stiffness" as well as daily activity, participation in sports, golf, etc. was recorded by the patients.

Notes were made as to the use of a cane or a knee brace. The patient's opinion of their condition in comparison with their initial state (the same, a little better, a lot better, worse, much worse) was recorded. The physician's evaluation was also made at the time of each visit (excellent, good, no change). Notes were made as to tolerance of Perna and compliance. Notes were also made in reference to the use of NSAIDS (nonsteroid anti-inflammatory drugs), pain medication, topical creams or ointments.

X-ray Evaluation

Standing, weight bearing AP views of both knees were taken initially, at two months, six months and one year. A special platform was built so that the patient could be positioned in a standard and reproducible manner. The radiographic tube was positioned so the central ray of the X-ray beam was horizontal and parallel to the floor. The tube was kept set 80 cm distance from the X-ray cassette. The center of the X-ray beam with the aid of the tube positioning light was focused on the center of the patient's patella.

In order to keep the same position for subsequent films of the same patient, an outline of the patient's feet was made with the patient standing on his/her own X-ray folder. This folder was always placed by the X-ray technician in exactly the same position on the platform.

The patients were prescribed three Perna capsules (a total of 1500 mg of *Perna canaliculus*), per day taken with food, then two capsules per day as permanent maintenance dosage. The product used in the study contained 500 mg green-lipped mussel (Perna) and 100 mg alfalfa.

The study was designed to last one year. Most patients continued to be followed subsequent to that time. Out of 120 original patients only eleven patients eventually elected total knee replacement. Most of the other patients continued to do well and continued to take the Perna capsules (two daily) for ongoing metabolic and chondro-protective support.

Patient Assessment

The patients were seen for follow-up one month after the initial visit. Subsequent to that date, depending on their program, they were seen every two to three months. A final assessment was made after one year.

X-rays of the patients were graded on the basis of a scale of I to IV using the Kellgren and Lawrence system - Degree of osteoarthritis progressing by grade from Grade 1, minimal, least severe, to Grade IV being bone on bone. The grade of severity in this group is described as follows:

	Grade according to Kellgren & Lawrence	*Number of Patients*
Increasing Severity of Osteoarthrits ↓	I	25
	II	76
	III	12
	IV	7

The response to management in these groups of patients studied became evident at the time of the first follow-up visit. Many of the Grade I and II patients who had presented with an initial analogue pain scale of 7 reported a 0 to 2. These patients continued to remain comfortable and active during the rest of the study. Evidence of pain, heat and swelling was noted to be significantly diminished or absent during the remaining visits. Motivation in several patients was simply to get a new supply of Perna, to visit with the physician and to manifest curiosity as to possible improvement in X-rays. The two patients who were using canes no longer required them.

The age and sex of the patients, the presence of genu varus or genu valgus did not appear to have a significant relation to therapeutic response. The degree of severity of disease was important. Perna was seen to be very effective in Kellgren Grade I and II, less effective in Grade III and IV. Grade IV is bone on bone (most severe).

A significant number of patients were able to reduce their NSAID intake by 50% or more. Pain medication was also noted to be less as patients continued to be followed. Most patients reported that their condition was much improved. No patient complained that his problem was worse. Nine previous patients complained of side effects from Perna consisting of bloating, gas, indigestion, and the fishy taste. They were advised to take other products containing glucosamine and chondroitin sulfate and were not included in this study analysis.

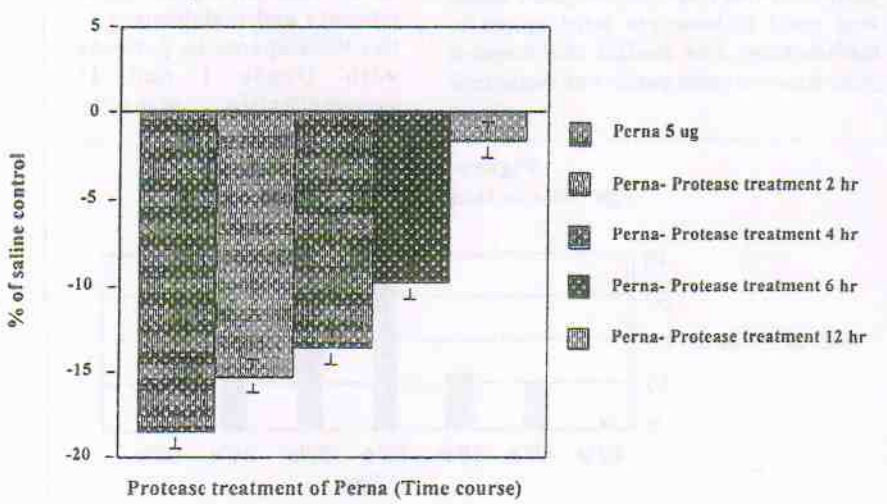
Patients remaining in this study (a total of 120) reported that they were either much improved (95) or some improved (16).

Nine of the patients in this study reported no change (Figure 12). According to this practitioner, nineteen (27%) showed no improvement (no change), thirty-eight (31%) showed good improvement and sixty-three (52%) were reported as having made excellent improvement (Figure 13).

No patients were lost at follow-up. This fact reflects the major difference from studies done in a university ➤

Figure 9

Time course effects of Protease treatment on Perna (Tween-20 extract) and its impact on IgG production levels of V2E9 hybridoma. Each data point represents a mean of three independent experiments with triplicate wells.



hospital outpatient facility. As the sole physician involved in this study, I became quite familiar with all of these patients, would recognize them on the street and would have a knowledgeable, up to date impression of their progress.

Seventeen patients in this study had previously undergone total knee replacement performed previously by the author. These patients were symptomatic on the unoperated knee and were anxious to avoid knee surgery if at all possible. Joint replacement is not accomplished without risk, the most common complication is component wear and loosening. None of these patients required additional total knee reconstruction.

Eleven patients in this study did eventually come to joint replacement therapy but felt that the Perna protocol had bought them some time. These patients were scheduled for surgery after the initial study period limit, one year. Five patients eventually required arthroscopic debridement. Seven patients have had intra-articular injection of hyaluronic acid. Five of them with good results. Two patients however, developed an acute foreign body reaction which necessitated total knee replacement.

X-ray Findings – Reversal of Progressive Joint Space Narrowing[35,36]

Radiographic evaluation showed that some patients had reversal of the narrowing of the joint space of the tibial femoral joint. An architect's caliper with a stabilizing screw and sharp points placed on the radiographic joint space was used to measure joint space in millimeters. The medial tibiofemoral joint space in genu varus was measured at Point C and P. Point C being the narrowest space in the joint, P being the most medial edge of the femur (Figure 14) Lateral measurements were made in osteoarthritic knees of patients with both genu valgus and genu varus. As an example, standing X-rays of a 53 year old male and a 51 year old female taken at different times are shown in Figure 15 and 16.

Eight patients in this study were found to have reversed the progressive joint space narrowing usually found in osteoarthritic patients as seen by X-ray analysis. The male patient in Figure 15 had a reversal of 1.2 mm in the joint spacing in Point C (3.0 mm on 7/25/97 versus 4.2 mm on 10/11/98). The female patient in Figure 16 also had a reversal of 1.2 mm in the joint spacing at Point C (3.0 mm on 1/30/98 versus 4.2 mm on 7/3/99). Lequesne reported a mean joint space loss in Point C of 0.26 mm per year is typical for patients with osteoarthritis of the knee.[35] Patients in this study with Grade I or II osteoarthritis were not found to show increased joint space narrowing during the course of the one year study. X-rays of patients with Grade III and IV did show evidence of increased joint space narrowing although the two Grade III patients given as examples actually showed reversal. All patients who required joint reconstruction were found to be rated as Grade IV, bone on bone.

Chondrogenesis – Regrowth of Articular Cartilage

X-ray findings showing a reversal of progressive joint space narrowing in eight patients and stabilization of the joint spaces in patients with Grade I and II osteoarthritis strongly suggested an anabolic effect of Perna stimulating chondrogenesis. This was supported by the findings in one patient at the time of arthroscopic debriedment. This patient was found to have a large ostiochondral defect, which appeared to have been overgrown by new viable cartilage. The appearance was as if the defect had been filled with a fresh latex paint.

Biomechanical Effects

Patients are seldom found who have been previously evaluated and treated for biomechanical factors involved in their disease process. Experience has shown that many patients benefit from having the appropriate wedges put into their shoes. Fortunately, present day shoe wear is sensible and most shoes can be worked with by a competent shoe maker. High heels must be avoided. The patients with Grade I or II arthritis respond to this simple regime and may expect to decrease their use of NSAIDS. The continued use of Perna capsules and

Figure 10
Age Distribution of Patients

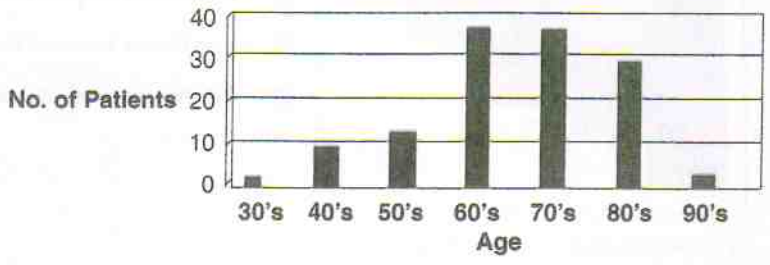


Figure 11
Pain distress intensity scale. (visual analogue)

the shoe wedges is a permanent recommendation for proper management of osteoarthritis of the knee.

Most patients are not happy with bracing and orthotics although the present day state of the art is excellent. Techniques for developing unloader braces for relief of the genu varus - genu valgus stress are quite effective. Compliance is difficult to obtain unless a patient is determined to avoid surgery.

Intra-articular Injection of Hyaluronic Acid

Intra-articular injection of hyaluronic acid benefited a few patients in this study group and in some cases, quite significantly. Most patients with Grade III or IV have not experienced lasting benefit from this procedure. Three patients out of thirty patients developed an acute inflammatory reaction to the injection. Two of these required total knee replacement and were found to have clinical evidence of an acute foreign body reaction.

Arthroscopy

Arthroscopy has definitely guided decisions made as to whether the patient may benefit from a high proximal tibial osteotomy. Upper tibial osteotomy, by various techniques is a widely accepted method of treatment for osteoarthritis of the knee. The major disadvantage of this operation is that no foreign material is implanted. Thus for younger patients who wish to continue playing sports or to engage in occupations requiring vigorous activity it is a satisfactory surgical procedure. The disadvantage is that if the arthritic process is too far advanced, the procedure may not have long-lasting effects. If there is arthroscopic evidence of cartilage loss, osteochondral fracture etc., total joint replacement has been recommended as the treatment choice.

Discussion of Results

The positive response of patients with gonarthrosis of the knee utilizing Perna mussel in this study was most encouraging. As a result, a modified approach to management of these patients in office practice has evolved. This overall approach is best expressed by the following algorithm.

As mentioned, after the initial patient history and complete physical examination of including X-ray examination, all patients in this study were started on the *Perna canaliculus* regime. Most had been on NSAIDS and were allowed to continue. If not, they were started on an appropriate NSAID. If pain was expressed as above 5 on the visual analogue scale an intra-articular injection of cortisone was administered. In office practice it is important that the patient experience relief as soon as possible. All patients who were 5 and under on the visual pain analog scale were completely stabilized using Perna and appropriate shoe wedges. This represented the vast majority of the patients in the study (101 out of 120) who were rated as Grade I or Grade II.

The benefits of the freeze-dried lyophilized Perna powder as a safe and effective anti-inflammatory agent, immune modulator and joint regenerative product in the office management of gonarthrosis has proven to be reliable. In this study a number of patients were significantly able to reduce their NSAID intake and pain medication dosage and maintain a more active lifestyle using a maintenance program of 1000 mg of Perna per day.

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Figure 12
Patient Assessment

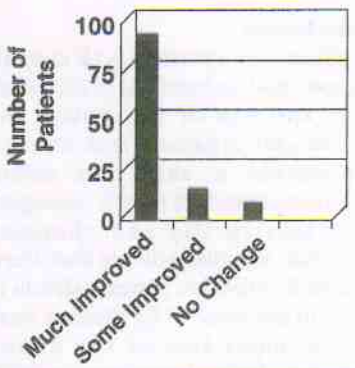


Figure 13
Practitioner Assessment

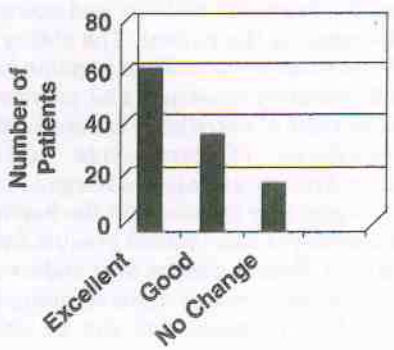
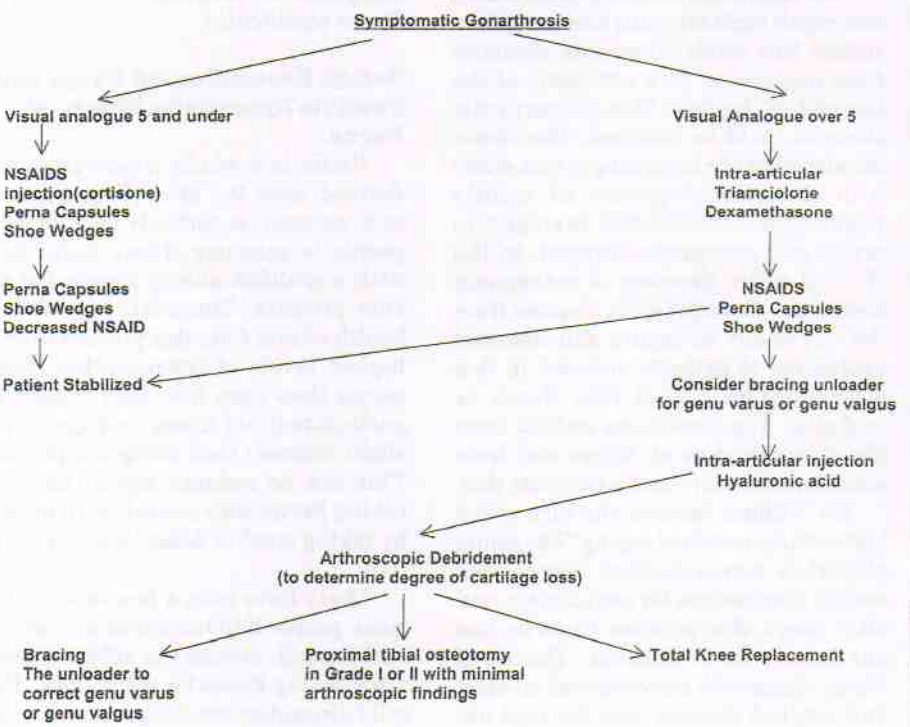


Figure 18 - Algorithim in Treatment of Gonarthrosis



Perna has been shown to be especially effective in this clinical evaluation for Grade I and II Osteoarthritis, and less effective in Grade III patients. It was not effective in Grade IV osteoarthritis where the damage had progressed to bone on bone. A possible alternative to orthodox therapy in the orthopedic management of gonarthrosis patients by a practicing orthopedist has been outlined in the algorithim above.

In general, management of arthritis of the knee in office practice tends to be realistic. Arthritis is considered to be chronic and incurable, a normal consequence of aging caused by "wear and tear" of joints. The physician does well to recall the traditional aim of treatment "To cure a few, to help many, and to comfort all."

This study suggests that osteoarthritis can be reversible. The very apparent and continued response of Grade I and II arthritis to the use of Perna mussel shows that cartilage has the innate ability to regenerate itself. Arthroscopic and radiographic evidence on ten patients strongly suggests that *Perna canaliculus* contributed to new growth of cartilage.

Overview by Dr. Hurley

The dogma that cartilage cannot heal and repair itself may be a misconception. Before this study there was evidence from experience with ostiotomy of the hip and of the knee that ostioarthritic changes could be reversed. The thesis developed at the beginning of this study was that the sequence of events resulting in osteoarthritis is subject to arrest and sometimes reversal, in the clinical office practice of orthopedic medicine. The experience gleaned from the day to day subjective and objective evaluation of patients included in this study suggests that this thesis is probable. The experience gained from the objective view of X-rays and from arthroscopic intervention suggests this.

Sir William Osler at the turn of the last century is quoted saying "The young physician leaves medical school with twenty medications for each disease and after years of experience finds he has one remedy for 20 diseases." The use of Perna along with conventional medical and surgical therapy over the past ten years, following a previous 30 years of clinical experience reminds one of the validity of this statement. I now prescribe nonsteriodal anti-inflammatory drugs, as well as muscle relaxants and pain medications to a much lesser degree.

Perna canaliculus has proven to be helpful in managing athletic injuries, fractures, particularly hip fractures in elderly osteoporotic females, and back pain in general. Specifically, I have been pleased by the benefit obtained in patients afflicted with degenerative disk disease and facet arthrosis. This is understandable in view of the fact that the proteoglycan structure of the intervetebral disk differs very little from that of articular cartilage.

Perna has been an excellent alternative for patients who are prohibited from taking aspirin or aspirin-like drugs because they are on Coumadin, or are required to discontinue these medications because of scheduled elective surgery. I advise all patients who are scheduled for surgery to discontinue all NSAIDS at least two weeks prior to surgery because of the associated risk of bleeding. Perna has been shown to have an anti-inflammatory effect approximating that of Indocin (carageenan assay) and has made a difference in these patients. It seems reasonable to prepare clients prior to elective orthopedic surgery by placing them on a nutritional supplement program that includes *Perna canaliculus*.

Safety, Recommended Usage and Possible Synergistic Effects of Perna

Perna is a whole, freeze-dried food derived from the green-lipped mussel and, as such, is perfectly safe for most people to consume. Those individuals with a shellfish allergy should not use this product. There are no adverse health effects from this product even at higher levels of consumption. Some people (less than 10%) may experience gastrointestinal upset (indigestion or slight nausea) from using the product. This can be reduced significantly by taking Perna with a meal, with juice or by taking smaller doses throughout the day.

There have been a few reports that some people find increased tenderness and warmth around the afflicted joints after taking Perna for a few days. This mild discomfort usually passes after one to two weeks and may be an indicator that the product is working on the joint itself. Taking an analgesic product during this time period may be helpful. It is important to stay on the program until relief of symptoms occurs. Stabilization of the condition may take from one to three months depending on the severity of condition and the person's biochemical individuality.

Based on clinical experience, the recommended program for using Perna is to begin with 6 capsules (500 mg each) daily, 2 capsules with each meal. This dosage should be followed for approximately one month or until conditions or symptoms improve. Then the dose can be adjusted to 2-4 capsules daily as the situation warrants. A reduction in pain, reduced stiffness and greater joint mobility is generally experienced after three to six weeks on the product.

Recent evaluation in dogs indicate that when *Perna canaliculus* is combined with appropriate levels of Glucosamine Sulfate and Methylsulfonylmethane (MSM), faster and more effective results may be seen. A study is currently underway to evaluate the possible synergistic effect of combining these three chondo-protective agents into one product.

Conclusion

Ongoing research in both animal and human studies continue to demonstrate that the use of the entire *Perna canaliculus* organism (not an extract) represents a safe and effective nutritional product for the management of osteoarthritis and rheumatoid arthritis. Results indicate that Perna is especially effective against Grade I and II arthritis where the disease has not led to major loss of the articular cartilage. Preliminary results indicate that Perna is effective in reducing the pain and inflammation associated with the condition as well as promoting regeneration of articular cartilage which results in greater mobility and exercise tolerance in the patient. The ability of *Perna canaliculus* to down regulate pro-inflammatory cytokines and provide a wide array of nutritional factors for the rebuilding of connective tissue (chondroitin sulfates, collagen and glycogen) may help explain the healing properties of this natural product from the sea. Future studies now underway may provide greater understanding on how *Perna canaliculus* can be used

effectively against other inflammatory and autoimmune conditions, especially when combined with other proven chondroprotective agents.

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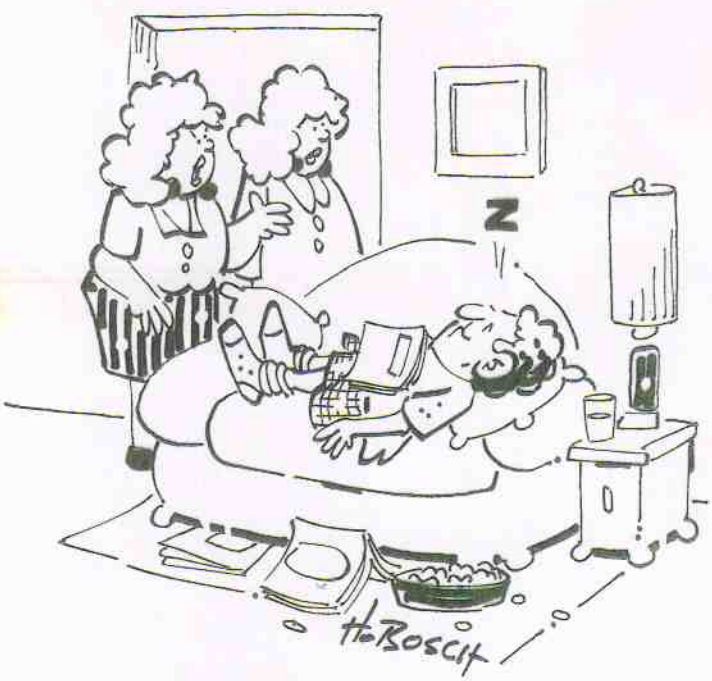

"Harold and I married for better or worse. Guess which one I got."