

Exhibit 1

EXHIBIT 1

Based on my review of the reliable and credible scientific literature regarding articular cartilage biochemistry and physiology, cartilage degeneration, degenerative joint disease and osteoarthritis, I conclude that there is significant scientific agreement in support of the following health claims:

- Glucosamine may reduce the risk of osteoarthritis.
- Chondroitin sulfate may reduce the risk of osteoarthritis.
- Glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis.
- Glucosamine may reduce the risk of osteoarthritis-related joint pain, tenderness and swelling.
- Chondroitin sulfate may reduce the risk of osteoarthritis-related joint pain, tenderness and swelling.
- Glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis-related joint pain, tenderness and swelling.
- Glucosamine may reduce the risk of joint degeneration.
- Chondroitin sulfate may reduce the risk of joint degeneration.
- Glucosamine and chondroitin sulfate may reduce the risk of joint degeneration,
- Glucosamine may reduce the risk of cartilage deterioration.
- Chondroitin sulfate may reduce the risk of cartilage deterioration.
- Glucosamine and chondroitin sulfate may reduce the risk of cartilage deterioration.

Composition and Physiologic Functions of Articular Cartilage and the Biochemical and Physiologic Roles of D-Glucosamine and Chondroitin Sulfate

Cartilage is composed of a complex extracellular matrix of collagen and elastic fibers within a hydrated gel of glycosaminoglycans and proteoglycans. This specialized network is stabilized by means of intermolecular and intramolecular cross-links that harness the swelling pressure exerted by the high concentration of negatively charged aggregates.¹ This accounts for more than 98% of the articular cartilage volume; cellular components constitute the remaining 2%. The interaction of these matrix components imparts the characteristic biomechanical properties of flexibility and resistance to compression. The collagen component of the cartilage matrix is relatively inert, but the other constituents, such as proteoglycans, undergo a distinct turnover process during

which the catabolism and removal of molecules from the extracellular matrix is in balance with the synthesis and deposition of new molecules.²

Proteoglycans are large macromolecules consisting of multiple chains of glycosaminoglycan disaccharides and oligosaccharides attached to a central protein core that provide a framework for collagen and also bind water and cations, forming a viscous, elastic layer that lubricates and protects the cartilage tissue. The presence of these negatively charged aggregates imparts to the matrix of articular cartilage its strong affinity for water and is the most significant contributor to the biomechanical properties of cartilage. The glycosaminoglycans most common in human connective tissue include the disaccharides keratan sulfate, dermatan sulfate, heparin sulfate and chondroitin sulfate and the oligosaccharide, hyaluronan. They consist of amino sugars, which are repeating disaccharide units composed of a hexuronic acid (D-glucuronic acid, iduronic acid, or L-galactose) and a hexosamine (D-glucosamine or D-galactosamine).^{3,4}

The main disaccharide units of cartilage glycosaminoglycans are formed by the (1→3) linkage of D-glucuronic acid to *N*-acetylglucosamine; disaccharide units are linked by β(1→4) galactosamine links. The D-galactosamine residues are sulfated either in position 4 (as in chondroitin-4-sulfate) or 6 (as in chondroitin-6-sulfate). The sulfate groups, together with the carboxyl groups of D-glucuronic acid, are ionized at tissue pH, conferring to the chain a strong global electronegative charge.⁵⁻¹⁰ Inadequate sulfate availability resulting in the production of undersulfated proteoglycans will reduce their electronegative charge and water carrying capacity.^{11,12}

Glucosamine (2-amino-2-deoxyalpha-D-glucose) is an aminomonosaccharide that serves as a substrate for the biosynthesis of chondroitin sulfate, hyaluronan, and other macromolecules located in the extracellular cartilage matrix. The conversion of L-glutamine and D-fructose-6-P to L-glutamate and D-glucosamine by L-glutamine-D-fructose-6-P amidotransferase (E.C. 2.6.1.16) is the rate-limiting step in proteoglycan synthesis.¹³⁻¹⁵ This reaction may be bypassed if D-glucosamine is available within the cell cytoplasm.^{16,17} Whatever its source, D-glucosamine is phosphorylated and the resulting D-glucosamine-6-P is acetylated to *N*-acetyl-D-glucosamine, the common precursor for the biosynthesis of keratan sulfate, dermatan sulfate, chondroitin sulfate and hyaluronan.^{16,17}

Chondroitin sulfate is a glycosaminoglycan that is polymerized into long, unbranched polysaccharide chains in which some of the constituent chondroitin moieties (composed of D-glucuronic acid and *N*-acetyl-D-glucosamine) are sulfated.¹⁸ Close control of chondroitin sulfate synthesis determines chain length, disaccharide composition and degree of sulfation, which vary with anatomic location, stage of development and age and are heterogeneous.¹⁹⁻²⁴ For example, the sulfation pattern of chondroitin disaccharides in normal human articular cartilage varies. The deeper layers of immature cartilage contain 4 times more sulfated residues than the upper regions of the immature tissue contain (as a result of polysulfation of some chondroitin residues in the extracellular matrix of the deeper regions).¹⁹⁻²¹ All regions of the extracellular matrix of immature articular

cartilage contain a smaller ratio of chondroitin-6-sulfate to chondroitin-4-sulfate than is typical of the extracellular matrix of articular cartilage in adults.¹⁹⁻²¹

Chondroitin sulfate polymers are secreted into the extracellular matrix covalently bound to proteins, forming protein-polysaccharide complexes called proteoglycans. In a proteoglycan, about 100 chondroitin sulfate chains, each containing 50 to 60 disaccharide units of chondroitin sulfate, are covalently attached to a polypeptide backbone composed of over 2,000 amino acids (the serine-rich core protein with a molecular weight of 250,000 to 300,000 daltons). This covalent *O*-linkage occurs between a terminal D-xylose or D-galactose residue that had been added to the polysaccharide chain and a serine or threonine residue on the core protein, with one chondroitin sulfate chain per 20 or so amino acid residues. The total molecular weight of an individual proteoglycan monomer is 1,500,000 to 2,500,000 daltons.⁵

One end of the core protein of a proteoglycan is non-covalently linked to a long polysaccharide filament of hyaluronan through a link protein; the connection is achieved by a globular region of the link protein that surrounds the terminal portion of the core protein and a stretch of 5 disaccharide units along the length of the hyaluronan chain.^{25,26} There are two structurally related N-terminal globular domains, G1 and G2, of which only G1 (and not G2) is involved in the aggregation of proteoglycans with hyaluronan. The interglobular domain joining G1 and G2 contains proteinase-sensitive sequences which appear to be the key sites for cleavage during aggrecan turnover.⁵ Approximately 100 core proteins are bound to an individual hyaluronan chain, at regular intervals of 300 Å, forming a unit of aggrecan, the large molecular mass proteoglycan-hyaluronan aggregate predominant within the extracellular matrix of articular cartilage.

The hydrodynamic properties of this aggregate determine the load-bearing capacity of articular tissue. As the electronegative charges of aggrecan draw water into the tissue, a large osmotic swelling pressure is created that swells and expands the extracellular matrix. This pressure produces tension within the interlacing collagen network of the matrix; balance is achieved when tension in the collagen network prevents further entry of water. Articular cartilage tissue swollen with water expresses substantial compressive resilience and offers considerable resistance to fluid flow and redistribution of water. Fully hydrated articular cartilage tissue behaves as a stiff elastic polymer when exposed to sudden impact loading, with pressure-induced displacement of water from the matrix with little or no effect on matrix macromolecules (although sustained loads will produce slow inelastic deformation). Removal of loading allows re-entry of water and a return to the pre-loading high-tension equilibrium condition.^{5,18,27-29}

Age and the Composition of Articular Cartilage

In rabbits, fetal articular cartilage is softer than is adult articular cartilage because fetal articular cartilage contains a greater proportion of polysulfated chondroitin sulfates and therefore its water binding capacity is greater.³⁰ In rats, as age increases from birth to

mature adulthood, the extent to which nonosteoarthritic articular cartilage extracellular matrix chondroitins are sulfated decreases significantly.³¹ In dogs, increasing age is accompanied by significantly decreased chondroitin sulfate and proteoglycan content of articular cartilage and reduced aggregability of the remaining proteoglycans.³² Similarly, calf articular cartilage proteoglycans are larger on average than are proteoglycans in nonosteoarthritic adult bovine articular cartilage (and contain larger chondroitin sulfate polymers).³³ In addition to decreasing average size of matrix proteoglycans and chondroitin polymers, the ratio of chondroitin 6-sulfate to chondroitin 4-sulfate in the extracellular matrix of articular cartilage increases with increasing age.³⁴

In humans, increasing age is accompanied by a decreasing proportion of chondroitin sulfates in the extracellular matrix of nonosteoarthritic articular cartilage³⁵ and increases in the ratio of chondroitin 6-sulfate to chondroitin 4-sulfate^{36,37} and in the free glucosamine content of the tissue.³⁸ Furthermore, the average chondroitin sulfate content of individual articular cartilage proteoglycans decreases, impairing the ability of proteoglycans to aggregate spontaneously with hyaluronan.³⁹ In addition, the ability of proteoglycans to aggregate spontaneously with hyaluronan is decreased as a result of an increased incidence of defect in the core protein of newly-synthesized proteoglycans.⁴⁰ Consequently, the aggrecan content of the extracellular matrix of articular cartilage in adults is significantly lower than that in children.⁴⁰

In "normal but aged" human chondrocytes (mean age of donor: 68.8 +/- 4.2 years), basal (unstimulated) synthesis of matrix-degrading stromelysin-1 and collagenase is significantly greater than in chondrocytes harvested from joints of "normal young adults" (mean age of donor: 28.6 +/- 7.1 years). Therefore, "aging" may sensitize chondrocytes to the effects of accelerators of extracellular matrix degradation and may increase the requirement of chondrocytes for exogenous substrate to support the synthesis of new and replacement matrix macromolecules.⁴¹

Precipitating Events Producing Cartilage Degeneration and Mechanical Failure

Osteoarthritis is a multifactorial, polygenic disorder involving mechanical, biochemical, environmental, systemic and genetic factors that contribute to imbalance between synthesis and degradation of cartilage matrix.^{42,43} Chronic imbalance in matrix macromolecule turnover producing net loss of articular tissue is a required precursor to the development of osteoarthritis and joint pain.

There are numerous potential etiologic triggers that can initiate the progression of events culminating in tissue failure. For example, quadriceps muscle weakness significantly increases the risk for osteoarthritis in humans⁴⁴ and laxity in a joint may precede failure of the cartilage matrix.⁴⁵ Interstitial fluid pressurization during loading contributes more than 90% of load support, shielding the collagen-proteoglycan matrix from excessive stresses and reducing friction at the articular surfaces.⁴⁶ A chronic imbalance of shock-

absorbing and weight-bearing muscles affecting joint alignment^{47,48} or overloading from excessive body weight⁴⁹ induces a mild yet chronic metabolic imbalance in the affected articular cartilage.

Whenever mechanical stress exceeds the tissue's load-bearing capacity, chondrocyte and synoviocyte secretion of the cytokines interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) and nitric oxide (NO) is stimulated. These cytokines auto-stimulate chondrocyte and synoviocyte secretion of matrix metalloproteinases (collagenase, gelatinase, aggrecanase, elastase, and fibronectin-degrading stromelysin-1) and inhibit chondrocyte synthesis of cartilage-specific proteoglycans and type II collagen. The resulting imbalance between synthesis and degradation of extracellular matrix components results in a net decrease in matrix content of aggrecan, type II collagen and other matrix macromolecules.^{42,43,50}

IL-1 β , IL-6, TNF- α and nitric oxide also stimulate the clonal expansion of chondrocytes whose daughter cells may express a "fetal" differentiation pattern during early metabolic imbalance in articular cartilage⁵¹ and produce inferior repair matrix prone to fibrillation and mechanical failure.^{42,43} Spontaneous repair matrix produced in early asymptomatic subclinical osteoarthritic change exhibits a heterogeneous composition more closely resembling that of fibrous cartilage,⁵² with inferior biomechanical competence^{53,54} resulting in functional incompetence and perishability.⁵⁵ In addition, the abnormal newly-synthesized matrix may be fibronectin-deficient or may undergo accelerated hydrolysis of fibronectin by stromelysin-1, in either case disturbing chondrocyte anchorage to the extracellular matrix ("anchorage dependence") and inducing apoptosis and hypocellularity (chondrocyte survival requires attachment to substrate).^{42,43}

In early asymptomatic subclinical osteoarthritic change in humans, reactive proliferation of extracellular articular cartilage matrix results in the production of abnormally large and more extensively sulfated chondroitin sulfate polymers and significantly decreased total glycosaminoglycan content (similar to the matrix of nonosteoarthritic human articular cartilage after partial enzymatic hydrolysis⁵⁶) and significantly decreased proportion of proteoglycans of nonosteoarthritic molecular sizes.⁵⁷⁻⁶⁰ Overall, there is a significantly increased proportion of nonaggregated proteoglycans, significantly decreased average size of proteoglycan aggregates (aggrecan) and incorporation of significantly smaller-than-normal-for-age chondroitin sulfate chains into newly-synthesized proteoglycans, significantly decreased total chondroitin sulfate content (and therefore decreased water binding capacity), and a significantly lower ratio of chondroitin 6-sulfate to chondroitin 4-sulfate.^{21,61-63} Both the abnormally small proteoglycans and the abnormally large proteoglycans are unable to aggregate with hyaluronan to form aggrecan.⁶⁴ In addition, osteoarthritic human articular cartilage exhibits increased synthesis of more readily hydrolyzable (easily degradable) collagens.^{65,66}

In cell culture, human articular chondrocytes harvested from osteoarthritic joint cartilage produced proteoglycans that differed from those produced by human articular

chondrocytes harvested from nonosteoarthritic joint cartilage.⁶⁷ These proteoglycans resembled “fetal-type” proteoglycans with increased chondroitin 4-sulfate content and an increased percentage of smaller proteoglycans than is typical of the proteoglycans produced by chondrocytes harvested by nonosteoarthritic human articular cartilage.⁶⁸ The synthesis of temporally inappropriate proteoglycans is accompanied by a significantly accelerated rate of degradation of older, more typical-for-age proteoglycans.⁶⁹

In a rat model of the initiation of osteoarthritic change, increased mechanical stress on articular cartilage increases the ratio of chondroitin 6-sulfate to chondroitin 4-sulfate in the extracellular matrix.⁷⁰ Mechanical compression of articular cartilage stimulates intrachondrocytic cyclo-oxygenase activity, resulting in increased production of PGE₂, an inducer of inducible NO synthase-2 (iNOS) activity; consequently, intrachondrocytic NO production is increased in proportion to the magnitude of compression and increasing local compression increases the recruitment of compression-responsive NO-producing articular chondrocytes.⁷¹ NO stimulates chondrocytic synthesis of matrix metalloproteinases,⁷² nascent (inactive) IL-1 β ,⁷³⁻⁷⁵ and interleukin-1-converting enzyme (ICE).⁷⁶ ICE activates nascent inactive IL-1 β .⁷⁵ Activated IL-1 β inhibits chondrocytic synthesis of proteoglycans^{73,74} and collagen^{73,74} and stimulates chondrocytic synthesis of stromelysin-1,⁴¹ collagenase⁴¹ and a presumptive aggrecanase enzyme that cleaves aggrecan.⁷⁷ As osteoarthritic change progresses, IL-1 β also stimulates increased NO production;⁷⁸⁻⁸¹ NO further stimulates chondrocytic synthesis of matrix metalloproteinases⁷² and accelerates the progression of osteoarthritis through the establishment of a cooperative positive feedback cycle.^{82,83} In addition, chondrocytes harvested from osteoarthritic human articular cartilage synthesize growth-related oncogene- α (GRO- α) in response to IL-1 β ; GRO- α stimulates degradation of fibronectin by stromelysin-1, producing anoikis (cell death resulting from loss of normal cell-substratum contact).⁸⁴

Chondrocytes harvested from osteoarthritic human joints exhibit a reduced anabolic response to insulin-like growth factor-1 (IGF-1) (“IGF resistance”,^{42,85}) and may have reduced ability to transport glucose from the extracellular fluid into the cell for glycosaminoglycan synthesis.⁸⁶ Therefore, osteoarthritic chondrocytes may have an increased requirement for glucosamine of extracellular origin.^{42,87-89} In addition, IGF-1 stimulates net synthesis of proteoglycans able to form aggrecan by nonosteoarthritic adult bovine articular chondrocytes in cell culture.⁹⁰ “IGF resistance” may contribute to the etiology of osteoarthritis by down-regulating the production of replacement aggrecan.

Oxidative stress also may impair the synthesis of matrix macromolecules by articular chondrocytes. Inhibition of chondrocyte γ -glutamyl-cysteine synthetase results in reduced intrachondrocytic glutathione concentration and decreased incorporation of sulfate into newly-synthesized proteoglycans and of proline into newly-synthesized collagen.⁹¹

Chronic Degeneration of the Extracellular Matrix of Articular Cartilage is a Required Precursor to Osteoarthritis

Changes in the macromolecular composition of the extracellular matrix of articular cartilage are characteristic of clinically apparent osteoarthritis. The ratio of chondroitin 6-sulfate to chondroitin 4-sulfate in the extracellular matrix of the articular cartilage of osteoarthritic mice is significantly greater than the ratio in the extracellular matrix of articular cartilage in age-matched nonosteoarthritic mice.⁹² Osteoarthritic rat articular cartilage, compared to nonosteoarthritic articular cartilage, exhibits significantly decreased total proteoglycan, chondroitin 4-sulfate and chondroitin 6-sulfate contents and significantly increased stromelysin-1 (fibronectin-degrading) activity.⁹³ In addition, the percentage of apoptotic chondrocytes in the tissue is significantly increased.⁹³ Proteoglycans in osteoarthritic adult bovine articular cartilage are larger than normal adult bovine articular cartilage proteoglycans (with larger chondroitin sulfate polymers) and closely resemble proteoglycans found in the articular cartilage matrix of calves.³³ Osteoarthritic equine articular cartilage contains a significantly increased proportion of unsulfated disaccharides and a significantly decreased proportion of chondroitin 6-sulfate.⁹⁴ The articular cartilage of *Cynomolgus* macaque monkeys with arthritis exhibits increased production of abnormal chondroitin sulfate-containing polymers.⁹⁵

In degenerative joint disease in dogs, affected articular cartilage contains significantly increased amounts of newly-synthesized large chondroitin sulfate-rich and glucosamine- and galactosamine-poor proteoglycans typical of those produced by immature canine articular cartilage.^{61,96,97} As cartilage degeneration progresses, affected canine articular cartilage exhibits significantly increased production of abnormal chondroitin sulfate-containing polymers, significantly increased water content, significantly increased proteoglycan content, significantly increased percentage of smaller proteoglycans and significantly decreased percentage of chondroitin sulfate in proteoglycans.^{57,98,99} Some newly synthesized proteoglycans are abnormally large (containing abnormally long chondroitin sulfate chains) and a second population of proteoglycans are abnormally small; both have lost the ability to aggregate spontaneously with hyaluronan, compromising the hydrodynamic properties of the tissue.¹⁰⁰

Pathologic changes in cartilage matrix composition and organization alter the affinity of the matrix for water and produce excessive cartilage deformation under loading.^{101,102} When chronic, excessive tissue deformation induces adaptive structural and compositional changes that confer increased stiffness in the tissue,⁴⁵ increasing its vulnerability to the compressive, tensile and shear forces that occur during normal joint function.¹⁸ Grossly apparent cartilage erosion does not appear until the tissue has lost considerable stiffness and is undergoing progressive mechanical failure.⁴⁵

As a result of the changes occurring in articular cartilage, abnormally transmitted mechanical stress produces microfractures within the tissue matrix that in turn increase the stresses on surrounding tissue and induce increased chondrocyte secretion of metalloproteinases.¹⁰³ The subsequent enzymatic tissue degradation potentiates local tissue stress and initiates a positive feedback loop. Increased loading on subchondral bone stimulates the attempt to reduce mechanical stress by increasing joint surface area through the production of bone spurs (osteophytes) at the joint margins (which confer the hard bony enlargement that is characteristic of chronic osteoarthritis).¹⁰³

The Culmination of Matrix Degeneration in Osteoarthritis

In the US, the incidence of at least one joint with osteoarthritis among those aged 15 to 40 years is about 5%; this increases to over 60% among those over 65 years old.¹⁰⁴ Overall, the prevalence of at least mildly symptomatic osteoarthritis in at least one joint is about 30%.¹⁰⁵ Symptomatic osteoarthritis of the knee occurs in about 6% of US adults aged 30 years and older,¹⁰⁶ although radiographic changes of the femorotibial compartment occur in 5% to 15% of people aged 35 to 74 years.¹⁰⁷

Clinical osteoarthritis (also known as degenerative joint disease) is characterized by focal loss of cartilage and hypertrophic bone spurs.¹⁰³ Although the term osteoarthritis refers to the overgrowth of bone at the margins and subchondral areas of the joint, and despite the eventual bony involvement in later stages of the disease, osteoarthritis is marked by net loss of cartilage tissue. Initial loss of articular cartilage tissue is mild but may progress to full thickness erosions and eventual bone-to-bone contact (loss of all joint space). Narrowing of the joint space may reflect other degenerative changes in addition to articular cartilage erosion;¹⁰⁸ as cartilage degeneration progresses, subchondral bone density and volume increase (consistent with increased transmission of load bearing into the subchondral bone).¹⁰⁹

The primary complaint in osteoarthritis is pain, particularly upon use of the affected joint.¹⁰³ Pain can be accompanied by varying degrees of joint stiffness, limitation of movement, tenderness and swelling at the joint margins and loss of function. Osteoarthritis often is asymmetric. There are no systemic symptoms outside the affected joint.¹⁰³

Possible causes of pain in human osteoarthritis include osteophyte growth with stretching of the periosteum, increased intraosseous pressure, microfractures, ligament damage, capsular tension, meniscal injury and synovitis.¹¹⁰ Radiologically measured decrease in joint space is significantly correlated with increase in pain severity, although the clinical utility of pain assessment as an estimator of joint deterioration is under debate.¹¹¹

Bioavailability of Supplemental Glucosamine and Chondroitin Sulfate

D-Glucosamine: There are 3 forms of commercially-available D-glucosamine: D-glucosamine (MW: 179), D-glucosamine-HCl (MW: 270) and D-glucosamine sulfate (a derivative of the naturally occurring cartilage extracellular matrix constituent, aminomonosaccharide D-glucosamine;¹¹² MW: 456). Because of the differences in molecular size, 1500 mg of D-glucosamine-HCl provides as much D-glucosamine as is provided by 2600 mg of D-glucosamine sulfate or 1040 mg of D-glucosamine. A daily intake of 1500 mg of D-glucosamine sulfate is equivalent to a daily intake of between 15 and 30 mg/kg body weight.

In studies in rats, 90% to 95% of ingested D-glucosamine sulfate was absorbed intact into the blood and about 30% of newly absorbed D-glucosamine sulfate was incorporated into newly synthesized proteoglycans in articular cartilage tissues.^{113,114} In studies in humans, consumption of 314 mg of crystalline D-glucosamine sulfate was followed by the absorption of about 280 mg (about 90%) intact into the bloodstream; about 50% of this amount (about 140 mg) survived hepatic first-pass extraction intact.¹¹⁵ When the consumption of 1884 mg occurred as one bolus or in three divided intakes of 626 mg every 4 hours, there was no difference in total D-glucosamine sulfate bioavailability to systemic tissues (about 40% to 50% of the amount ingested). Other investigators have reported that over 90% of ingested D-glucosamine sulfate was absorbed intact into the human enterohepatic circulation.^{116,117} One investigator reported that about 75% of ingested D-glucosamine sulfate was bioavailable to body tissues following hepatic first-pass extraction.¹¹⁷

In healthy subjects, ingestion of D-glucosamine sulfate was followed by increased serum sulfate concentration. In contrast, ingestion of sodium sulfate did not effect serum sulfate concentration, suggesting that dietary supplementation with D-glucosamine sulfate might provide D-glucosamine, free sulfate and D-glucosamine sulfate for proteoglycan synthesis.¹¹⁸

Chondroitin sulfate: In dogs, rats, mice and rabbits, about 0% to 15% of an ingested mix of chondroitin sulfates was absorbed intact.^{42,119-124} In these species, absorption favors chondroitin sulfate polymers with molecular weights <14,000 daltons.¹²⁰ In all species studied, some inorganic SO_4^{-2} also was absorbed following cleavage of SO_4^{-2} from the chondroitin sulfate polymers by sulfatases.^{42,119-124}

In humans, between 0% and 15% of an oral bolus of chondroitin sulfates is absorbed intact into the blood.¹²⁵⁻¹²⁸ In addition, another 10% to 20% is absorbed following hydrolysis to smaller polymers (<5000 daltons) prior to absorption.^{128,129} However, the biological activity of these smaller polymers has been questioned.¹⁷ The absorption of chondroitin sulfates probably is not nil; the consumption of either 800 mg or 3000 mg of mixed chondroitin sulfates significantly increased plasma chondroitin sulfate concentration 3 hours after ingestion^{130,131} and the consumption of 800 mg daily for 5

days increased plasma chondroitin sulfate concentration from undetectable levels to a mean of 1.80 mcg/mL, suggesting that the systemic bioavailability of intact chondroitin sulfates in humans is about 12% of the amount ingested.¹³¹

Biochemical and Physiologic Roles of D-Glucosamine in the Preservation of Articular Cartilage

In cultures of chondrocytes harvested from nonosteoarthritic rat articular cartilage, IL-1 β inhibits the expression of UDP-glucuronosyltransferase I mRNA, resulting in decreased synthesis of proteoglycans and their precursors.^{132,133} Conversely, IL-1 β stimulates intrachondrocytic production of the catabolism-inducing factors, NO and PGE₂, resulting in increased expression of mRNA coding for the extracellular fibronectin degrading metalloproteinase enzyme, stromelysin-1.¹³² The addition of D-glucosamine to the culture medium prevented IL-1 β -induced inhibition of the expression of UDP-glucuronosyltransferase I mRNA^{132,133} and of proteoglycan synthesis,^{132,133} as well as IL-1 β -induced activation of pro-apoptotic nuclear factor KB (NF-KB).¹³³ The addition of D-glucosamine-HCl to the culture medium of nonosteoarthritic equine articular cartilage explants in organ culture prevented IL-1 β -induced increases in the activities of stromelysin-1, collagenase and gelatinase and bacterial lipopolysaccharide (LPS)- and IL-1 β -induced increases in the production of NO and PGE₂ and the degradation of extracellular matrix proteoglycans.¹³⁴⁻¹³⁷ Similarly, crystalline D-glucosamine sulfate added to the culture media of chondrocytes harvested from osteoarthritic human articular cartilage inhibited the inherent^{138,139} and IL-1 β -induced^{132,139} catabolic activity of metalloproteases secreted by the chondrocytes and stimulated the synthesis of physiologically-relevant proteoglycans with chemical characteristics of proteoglycans synthesized by chondrocytes harvested from nonosteoarthritic human articular cartilage.^{138,140} By unknown but presumably similar mechanisms, dietary supplementation with D-glucosamine sulfate (50 mg/kg body weight daily) conferred to rats resistance to kaolin-and adjuvant-induced tibio-tarsal arthritis.¹⁴¹

Both D-glucosamine-HCl and D-glucosamine sulfate added to the culture medium of nonosteoarthritic rat femoral articular cartilage explants in organ culture significantly increased the rates of collagen and proteoglycan synthesis and partially prevented nonsteroidal anti-inflammatory drug- (NSAID)-induced inhibition of proteoglycan synthesis.¹⁴ Similarly, crystalline D-glucosamine sulfate stimulated the production of proteoglycans by chondrocytes harvested from nonosteoarthritic human articular cartilage in cell culture.¹⁴² When added to the culture media of chondrocytes harvested from osteoarthritic human articular cartilage, in which adhesion of chondrocytes to fibronectin and overall protein synthesis are significantly inhibited while extracellular collagenase activity is significantly increased, D-glucosamine restored the adhesive properties of the chondrocytes,¹⁴³ significantly reduced extracellular collagenase activity¹³⁸ and significantly increased the rate of protein synthesis.¹³⁸ Osteoarthritic articular cartilage tissue samples harvested from rabbits that had been fed diets supplemented with D-

glucosamine-HCl (20 mg/kg body weight daily) exhibited significantly accelerated rates of synthesis of new proteoglycans compared to articular cartilage tissue samples harvested from unsupplemented animals.¹⁴⁴

D-glucosamine appears to act by interrupting message transduction. Following transport across the chondrocyte cell membrane by the GLUT-2 and GLUT-4 glucose transporters,^{145,146} supplemental D-glucosamine stimulated the expression of IL-1 cell membrane receptor subtype II, which binds IL-1 β with high affinity but produces an inactive receptor-ligand complex, effectively intercepting IL-1 β -based signal transmission.¹³³ In addition, when D-glucosamine was added to the culture medium of nonosteoarthritic bovine articular cartilage explants in organ culture in concentrations that significantly inhibited IL-1 β -induced aggrecanase cleavage of aggrecan, lactate production was unaffected and D-glucosamine was incorporated into newly-synthesized chondroitin sulfates.¹¹³ D-Glucosamine-HCl also stimulated sulfate incorporation into chondroitin sulfates in the extracellular matrix of nonosteoarthritic bovine articular cartilage explants in organ culture.¹⁴⁷ In contrast, concentrations of D-glucosamine-HCl sufficiently high to compromise cell viability in nonosteoarthritic bovine articular cartilage explants in organ culture¹⁴⁸ or in nonosteoarthritic canine chondrocytes in cell culture¹⁴⁹ also significantly inhibited proteoglycan synthesis. These findings indicate that the inhibition of IL-1 β -induced catabolism was not an artefact of D-glucosamine-induced general inhibition of chondrocyte cellular metabolism.¹³⁹

In other cell culture models, D-glucosamine-HCl (0.01 to 1.0 mM) dose-dependently suppressed the superoxide anion generation induced by formyl-Met-Leu-Phe (fMLP) or complement-opsonized zymosan and inhibited the phagocytosis of complement-opsonized zymosan or IgG-opsonized latex particles.¹⁵⁰ Similarly, D-glucosamine-HCl significantly inhibited fMLP-induced up-regulation of CD11b, polymerization of actin, and activation via phosphorylation of pro-apoptotic p38 mitogen-activated protein kinase (MAPK).¹⁵⁰ In addition, D-glucosamine-HCl inhibited the release of lysozymes from phagocytosing neutrophils and suppressed neutrophil chemotaxis toward zymosan-activated serum.¹⁵⁰ Furthermore, supplemental D-glucosamine inhibited the activation of T-lymphocytes and the reactivity of leukocytes without producing signs of cellular toxicity.¹⁵¹ All of the effects of supplemental D-glucosamine provide evidence that its immunomodulatory, anabolic and anticatabolic properties result at least in part from interaction with intercellular and intracellular cytokine-based communication systems.

Biochemical and Physiologic Roles of Chondroitin Sulfate in the Preservation of Articular Cartilage

In cultures of chondrocytes harvested from nonosteoarthritic human knee joint articular cartilage, supplemental crystalline chondroitin sulfate polymers (Condrosulf[®], Sanova Pharma, Vienna, Austria; 55% chondroitin 4-sulfate, 38% chondroitin 6-sulfate, 5% unsulfated chondroitin sulfates, 1% disulfated chondroitin sulfates, 1% non-chondroitin

compounds, average molecular weight: 24,000 daltons) bind to a specific cell membrane receptor, possibly CD36, prior to transport into the chondrocyte cell cytoplasm.¹⁵² When added to culture media, both Condrosulf[®] and a synthetic mixture of chondroitin 4-sulfate and chondroitin 6-sulfate (Structum[®], Smith Kline Corp. Philadelphia, PA; undefined polydisperse mixture of chondroitin 4-sulfate and chondroitin 6-sulfate) significantly stimulated the production of proteoglycans by nonosteoarthritic human articular cartilage chondrocytes in cell culture.^{142, 153} Paradoxically, high concentrations (>1000 mcg/mL) of Condrosulf[®] in the culture medium induced concentration-dependent downregulation of the expression of mRNA coding for aggrecan.¹⁵⁴

An undefined mix of chondroitin sulfates stimulated significant increases in the secretion of proteoglycans in nonosteoarthritic cartilage tissue¹⁵⁵ and by embryonic articular cartilage chondrocytes in cell culture.¹⁵⁶ Chondroitin 4-sulfate alone added to the culture medium stimulated significant increases in the secretion of proteoglycans and in the incorporation of sulfate into chondroitin-containing proteoglycans by embryonic articular cartilage chondrocytes in cell culture.¹⁵⁷

A synthetic mixture of chondroitin 4-sulfate and chondroitin 6-sulfate (Structum[®]) prevented IL-1 β -induced inhibition of total proteoglycan synthesis by nonosteoarthritic human articular cartilage chondrocytes in cell culture.¹⁵³ Similarly, undefined mixtures of chondroitin sulfates (10 mcg/mL) prevented IL-1 β -induced inhibition of total proteoglycan synthesis¹⁵⁸ and IL-1 β -induced stimulation of stromelysin-1 activity¹⁵³ in cultures of nonosteoarthritic human articular cartilage chondrocytes. Individually, both chondroitin 4-sulfate and chondroitin 6-sulfate significantly inhibited the secretion of the endopeptidase, cathepsin B, by cultured nonosteoarthritic rabbit articular chondrocytes.¹⁵⁹ However, very low concentrations of undefined mixtures of chondroitin sulfates (<1 mcg/mL) failed to significantly inhibit PGE₂ secretion or bacterial LPS-induced production of NO by nonosteoarthritic equine articular cartilage tissue explants in organ culture either alone or when added to significantly inhibitory concentrations of glucosamine-HCl.¹³⁷ In contrast, concurrent exposure of chondrocytes harvested from nonosteoarthritic articular cartilage and grown in cell culture to chondroitin sulfate (100 mcg/mL) partially inhibited the pro-apoptotic effect of NO added in amounts that when added alone significantly increased the percentage of cultures chondrocytes undergoing apoptosis.¹⁶⁰ In the same model system, although concurrent exposure was ineffective, the addition of chondroitin sulfate to the culture medium 72 hours before the addition of sodium nitroprusside (SNP) prevented SNP-induced stimulation of NO production and cellular apoptosis.¹⁶¹

Diets supplemented with mixed chondroitin sulfates prevented chymopapain-induced degradation of knee articular cartilage in nonosteoarthritic rabbits.¹⁶² Dietary supplementation with chondroitin 6-sulfate (100 mg/kg body weight daily) significantly inhibited the destruction of articular cartilage following subsequent injection of type II collagen in Freund's adjuvant on day 14 in nonosteoarthritic mice¹⁶³ and significantly

inhibited the depletion of proteoglycans in articular cartilage following subsequent injection of bradykinin on day 14 in nonosteoarthritic rats.¹⁶⁴

Fragments of large chondroitin sulfate chains similar to those found in the blood after the oral ingestion of large chondroitin sulfate chains and their degradation prior to the absorption of the fragments significantly inhibited directional chemotaxis, phagocytosis and cytokine-stimulated release of lysozymes in human leukocytes *in vitro*.¹³¹ Both polydisperse mixtures of chondroitin sulfates^{165,166} and Matrix[®] (a defined mixture of 25% chondroitin 4-sulfate and 75% chondroitin 6-sulfate¹⁶⁷) inhibited the activity of human leukocyte elastase *in vitro*. The inhibitory activity was limited to chondroitin sulfate polymers larger in size than 2000 daltons,^{168,169} may be limited to chondroitin 6-sulfate¹⁷⁰ and increased with the degree of sulfation of the polymers.^{169,171} Although only an indirect indicator of events in cartilage, but consistent with an anticatabolic role for supplemental chondroitin sulfates, plasma elastase activity was significantly decreased in nonosteoarthritic rats following 8 days of dietary supplementation with a mixture of chondroitin sulfates (600 mg/kg body weight daily).⁵ A report that *in vitro* both chondroitin 4-sulfate and chondroitin 6-sulfate compete with hyaluronan for digestion by hyaluronidase suggests an additional role for supplemental chondroitin sulfates in the direct protection of articular cartilage extracellular matrix macromolecules from the elevated degradative enzyme activities characteristic of asymptomatic subclinical cartilage degeneration.¹⁷²

Supplemental D-Glucosamine and Osteoarthritis

Dietary supplementation with D-glucosamine-HCl (2000 mg/day) produced a significantly greater decrease in subjective pain assessment in 12 weeks than did placebo in adults with regular knee pain that had not yet progressed to clinically identifiable osteoarthritis.¹⁷³ However, there were no significant differences in the improvement in clinical or functional tests of joint motion and balance. In contrast, dietary supplementation with D-glucosamine-HCl (1500 mg/day) for 2 months was no better than the consumption of placebo in relieving joint pain in individuals with mild to severe femorotibial osteoarthritis.^{174,175}

On the other hand, in 2 randomized double-blind placebo-controlled clinical studies, compared to the effects of placebo, dietary supplementation of subjects with mild to severe femorotibial osteoarthritis with crystalline D-glucosamine sulfate (Dona[®]; 1500 mg/day) for 1 month has produced significantly greater reductions in articular pain, tenderness, swelling and restriction of movement.^{176,177} In another study, short-term dietary supplementation with Dona[®] (1500 mg/day) 4 weeks produced a significantly greater decrease in the Lequesne functional index of impairment and a significantly greater increase in the percentage of "responders" (subjects experiencing a decrease of at least 3 points in the Lequesne index) than did placebo.¹⁷⁸ Compared to subjects consuming placebo, subjects consuming D-glucosamine sulfate experienced no

differences in the incidence or severity of side effects or in the results of routine clinical chemistry, hematology, urinalysis, heart rate, blood pressure or body weight. Similarly, dietary supplementation with Dona[®] (1500 mg/day) for 6 to 8 weeks produced significantly greater decreases in joint pain, tenderness and swelling and in the number of days until improvement was noted in joint pain, tenderness or swelling as well as significantly greater increase in the percentage of patients experiencing some degree of improvement in joint pain, tenderness or swelling without producing differences in the incidence or severity of side effects or in hematologic or urinary variables, compared to the effects of placebo consumption.¹⁷⁹

In long-term randomized double-blind placebo-controlled clinical studies, compared to the effects of placebo, 3 years of dietary supplementation with Dona[®] (1500 mg/day) by subjects with mild to severe femorotibial osteoarthritis produced significantly greater reductions in the mean rate of femorotibial joint space narrowing (measured as the width of the medial femorotibial joint space, with the knee in full extension, by visual inspection; the “preferred, gold standard outcome” in studies of osteoarthritis¹⁸⁰), the WOMAC total pain score, the WOMAC indices of total knee health, pain, function and stiffness, the Lequesne functional index and pain assessed by a visual analog scale.^{180,181} In addition, the number of subjects experiencing “severe” (i.e., > 0.5 mm) joint space narrowing was significantly smaller after 3 years of dietary supplementation with D-glucosamine sulfate. However, among those subjects consuming D-glucosamine sulfate, those with less severe osteoarthritis at baseline tended to experience better responses. Furthermore, 3 years of daily dietary supplementation with 1500 mg of D-glucosamine sulfate produced no greater number or severity of side effects, including changes in the results of routine annual clinical laboratory examinations, than did 3 years of consumption of placebo.

In a far-ranging multicenter open-label study, a total of 1208 evaluable subjects were supplemented with Dona[®] (1500 mg/day) for 13 to 99 days.¹⁸² Physician ratings of subject responses were highly favorable: “good” (59% of subjects), “sufficient” (36% of subjects) and “insufficient” (5% of subjects). The best response was experienced by subjects with osteoarthritis of the knee or elbow, while those with osteoarthritis of the hip fared more poorly. The effect of D-glucosamine sulfate on pain scores was directly proportional to the duration of supplementation. In a more targeted open-label study, 69 young athletes (mean age 19 years) with cartilage degeneration of the knee (biochemically similar to osteoarthritis) received dietary supplementation with Dona[®] (1500 mg/day for 4 days, then 750 mg/day for 90 to 120 additional days.¹⁸³ After 120 days, complete remission of symptoms (patella-grinding sound, patella-displacement pain, patella-pressure pain) was reported for 76.5% of the subjects.

In two uncontrolled studies, subjects with femorotibial osteoarthritis were supplemented with either Dona[®] (1500 mg/day) or ibuprofen (1200 mg/day) for 4 weeks.^{184,185} In both studies, both groups experienced similar significant decreases in the Lequesne index of functional impairment¹⁸⁴ and in pain at rest, pain during movement, pain under loading and joint swelling¹⁸⁵ (compared to baseline). However, in both studies there were

significantly more adverse events and adverse event-related trial dropouts among the subjects consuming ibuprofen. In a similar uncontrolled study, subjects with femorotibial osteoarthritis were supplemented with either Dona[®] (1500 mg/day) or ibuprofen (1200 mg/day) for 8 weeks.¹⁸⁶ In this study, Dona[®] produced a significantly greater decrease in subjective assessment of knee pain with no difference in the incidence or severity of side effects.

Among subjects with osteoarthritis of the temporomandibular joint, D-glucosamine sulfate (Jamieson[™]; Windsor, Ontario, Canada; 1500 mg/day for 90 days) supplementation produced a significantly greater decrease in pain assessed using a visual analog scale compared to the pain relief afforded by ibuprofen (1200 mg/day for 90 days).¹⁸⁷ There were no significant differences between D-glucosamine sulfate and ibuprofen in the production of significant reduction in masticatory muscle pain and significant increases in pain-free mouth opening and voluntary mouth opening.

Several groups of investigators have applied the techniques of meta-analysis to evaluate dietary supplementation with D-glucosamine sulfate. One investigator concluded that the randomized double-blind placebo-controlled studies of adequate quality to include in the analysis demonstrated that dietary supplementation with D-glucosamine sulfate produced significantly greater reductions in the Lequesne Index of functional impairment, the severity of pain assessed using a visual analog scale and voluntary consumption of NSAID's for rescue from pain than did placebo (the effect sizes were "large").¹⁸⁸ In addition, it was concluded that D-glucosamine sulfate has demonstrated a consistently excellent safety profile.

Other investigators concluded that dietary supplementation with D-glucosamine sulfate by individuals with osteoarthritis consistently produced significant decreases in joint pain and significant increases in joint function of small-to-moderate magnitude,¹⁸⁹ that dietary supplementation with D-glucosamine sulfate is "probably effective in osteoarthritis in reducing pain and in improving joint function"¹⁰⁷ and that dietary supplementation with D-glucosamine sulfate (1500 mg/day) produces significantly increased pain relief in individuals with femorotibial osteoarthritis accompanied by an excellent safety profile.¹⁹⁰

When only "high quality" studies were considered by another investigator, it was concluded that dietary supplementation with D-glucosamine sulfate by individuals with osteoarthritis produced an approximately 50% reduction in pain with a similar improvement in function (a "large" effect consistently greater than that of placebo).¹⁹¹ However, it was noted that the quality of most published studies concerning dietary supplementation with D-glucosamine sulfate by individuals with osteoarthritis has been generally poor and that the magnitude of the reported effects of dietary supplementation with D-glucosamine sulfate are likely to be inflated by weaknesses in the study designs and analysis. Nonetheless, it was concluded that, despite their poor flaws, the available published studies demonstrate a significant degree of efficacy for dietary supplementation with D-glucosamine sulfate.¹⁹¹

Supplemental Chondroitin Sulfate and Osteoarthritis

In randomized, double-blind, placebo-controlled studies of subjects with femorotibial osteoarthritis ranging from mild to severe, compared to the effects of placebo, dietary supplementation with Condrosulf[®] (Sanova Pharma, Vienna, Austria; 55% chondroitin 4-sulfate, 38% chondroitin 6-sulfate, 5% unsulfated chondroitin sulfates, 1% disulfated chondroitin sulfates, 1% non-chondroitin compounds, average molecular weight: 24,000 daltons; 800 mg/day for 6 months,¹⁹² 1 year¹⁹³ or 2 years¹⁹⁴ or 1200 mg/day for 3 months¹⁹⁵ or 6 months¹⁹⁶) consistently produced significantly greater decreases in the Lequesne Index of functional impairment and in the severity of spontaneous joint pain assessed using a visual analog scale. After 1 year, subjects consuming 800 mg/day also exhibited significantly smaller increases in serum concentrations of osteocalcin (a biomarker of new bone formation) and keratan sulfate (a biomarker of proteoglycan degradation) and urinary excretions of pyridinoline and deoxypyridinoline (biomarkers of collagen degradation), although overall mobility and the mean rate of narrowing of the internal femorotibial space were not affected by dietary supplementation with chondroitin sulfates.¹⁹³ However, subjects consuming 800 mg/day for 2 years exhibited significantly smaller decreases in the mean internal femorotibial space.¹⁹⁴ In none of these studies did dietary supplementation with chondroitin sulfates produce a significant increase in the incidence or severity of side effects.¹⁹²⁻¹⁹⁶

In a randomized, double-blind, placebo-controlled study of subjects with osteoarthritis of the hip ranging from mild to severe, daily supplementation with Condrosulf[®] (1200 mg for 24 weeks) produced significantly greater decreases in the Lequesne Index of functional impairment, the severity of spontaneous joint pain assessed using a visual analog scale and the voluntary use of nonsteroidal anti-inflammatory drugs (NSAID's) for rescue from pain, although in this short-term study the mean rate of narrowing of the internal femorotibial space was not affected by dietary supplementation with chondroitin sulfates.¹⁹⁷ In a randomized, double-blind, placebo-controlled study of subjects with osteoarthritis of the interphalangeal joints, daily supplementation with Condrosulf[®] (1200 mg for 3 years) produced a significantly greater decrease in the number of subjects whose osteoarthritis had progressed.¹⁹⁸ However, there was no effect on the progression of osteoarthritis of the metacarpal joints. Even after as long as 3 years of daily supplementation there were no significant differences in the incidence or severity of side effects or adverse reactions.¹⁹⁸

In three short-term open-label studies, dietary supplementation with Condrosulf[®] (400 mg/day,¹⁹⁹ 800 mg/day²⁰⁰ or 1200mg/day²⁰¹ for 3 months) significantly reduced the severity of spontaneous joint pain assessed using a visual analog scale and the voluntary use of nonsteroidal anti-inflammatory drugs (NSAID's) for rescue from pain in subjects with osteoarthritis of the interphalangeal, femorotibial or hip joints. One study reported 97% subject compliance with supplementation²⁰⁰ and no study reported clinically significant side effects.

In a randomized, double-blind, placebo-controlled study of subjects with early mild femorotibial osteoarthritis, 2 years of dietary supplementation with Matrix[®] (25% chondroitin 4-sulfate and 75% chondroitin 6-sulfate; IRBI S.p.A., Rome, Italy; 800 mg/day) produced significantly greater decreases in the severity of spontaneous joint pain assessed using a visual analog scale and the voluntary use of nonsteroidal anti-inflammatory drugs (NSAID's) for rescue from pain.²⁰² In another randomized, double-blind, placebo-controlled study of subjects with early mild femorotibial osteoarthritis, 330 days of dietary supplementation with Matrix[®] (200 mg/day) produced significantly greater decreases in the severity of spontaneous joint pain assessed using a visual analog scale, pain on passive movement, pain on active movement, and pain in the evening; significantly greater increases in joint mobility and ambulation; and a significantly smaller decrease in mean articular cartilage thickness (measured echographically).²⁰³ In neither trial were the incidence or severity of side effects or adverse reactions significantly different among the subjects consuming Matrix[®] or placebo. Similarly, in an open label pilot study, dietary supplementation with Matrix[®] (1200 mg/day for 2 months) significantly reduced the severity of spontaneous joint pain assessed using a visual analog scale without producing side effects.²⁰⁴

Subjects with femorotibial osteoarthritis ranging from mild to severe have participated in three studies during which one group of subjects received supplemental Condrosulf[®] (800 mg/day) for 3 months, placebo for 3 months, Condrosulf[®] (800 mg/day) for 3 months and placebo for 3 months while a second group of subjects consumed only placebo for 12 months.²⁰⁵⁻²⁰⁷ In all 3 studies, after 12 months, despite having consumed only placebo for the 3 months prior, subjects previously supplemented with Condrosulf[®] exhibited significantly greater decreases in the Lequesne Index of functional impairment, the severity of spontaneous joint pain assessed using a visual analog scale and the mean rate of narrowing of the internal femorotibial space. In one study, the supplemented subjects also exhibited significantly smaller decreases in femorotibial joint articular surface area, femorotibial joint space volume and femoral articular cartilage thickness.²⁰⁶ In addition, between months 9 and 12 in this study (when both groups consumed placebo), unlike the subjects consuming placebo for 12 months, the subjects previously consuming Condrosulf[®] did not experience rebound increase in pain.²⁰⁶ In another study, after 12 months, despite having consumed only placebo for the 3 months prior, subjects previously supplemented with Condrosulf[®] exhibited significantly smaller increases in the serum concentration of cartilage oligomeric matrix protein (COMP) (a biomarker of synovial and cartilage inflammation), serum concentration of keratan sulfate (a biomarker of proteoglycan degradation), and urinary excretion of pyridinoline and deoxypyridinoline (biomarkers of collagen degradation), confirming the anticatabolic properties of supplemental chondroitin sulfates.²⁰⁵ In contrast, serum concentrations of osteocalcin were not significantly affected, suggesting that supplemental chondroitin sulfates do not actively influence bone metabolism or turnover.²⁰⁵ In none of the 3 trials were the incidence or severity of side effects or

adverse reactions significantly different among the subjects consuming Condrosulf[®] or placebo.²⁰⁵⁻²⁰⁷

The effectiveness of dietary supplementation with Condrosulf[®] in reducing pain has been compared directly to the effectiveness of NSAID's. Subjects with femorotibial osteoarthritis ranging from mild to severe were supplemented with either Condrosulf[®] (1200 mg/day) or diclofenac sodium (150 mg/day) for 3 months, after which both groups of subjects were supplemented with placebo for another 3 months.²⁰⁸ After 3 months of active supplementation, both groups of subjects exhibited similar significant decreases (compared to baseline) in the Lequesne Index of functional impairment, the severity of pain at rest assessed using a visual analog scale and the severity of pain on loading assessed using a visual analog scale. However, after 3 subsequent months of placebo, pain increased significantly in subjects previously supplemented with diclofenac sodium but did not increase in subjects previously supplemented with Condrosulf[®].

In two preliminary open-label studies, the diets of subjects with osteoarthritis of the femorotibial or hip joints were supplemented with 1000 mg/day to 1500 mg/day of Structum[®] (Smith Kline Corp. Philadelphia, PA; undefined polydisperse mixture of chondroitin 4-sulfate and chondroitin 6-sulfate) for up to 4 months.^{209,210} Supplementation was reported to have produced significant decreases in pain, with up to 85% of subjects reporting reduced pain and enhanced mobility.²¹⁰ When the diets of similar subjects were supplemented with 1000 mg/day of Structum[®] for 6 months, pain at rest disappeared completely in 57% of subjects with femorotibial osteoarthritis and in 46% of subjects with osteoarthritis of the hip and pain with movement disappeared completely in 17% of subjects with femorotibial osteoarthritis and in 13% of subjects with osteoarthritis of the hip.²¹¹ During the 6 months of this open-label study, joint function improved significantly while voluntary consumption of NSAID's for rescue from pain decreased significantly. In a similar 3-month placebo-controlled study, 1000 mg/day of Structum[®] produced significantly greater decreases in the Lequesne Index of functional impairment, the severity of pain at rest assessed using a visual analog scale and voluntary consumption of NSAID's for rescue from pain.²¹² After 3 subsequent months of discontinuation of supplementation, no significant return of pain occurred among the previously-supplemented subjects. There were no clinically significant side effects in any reported study of dietary supplementation with Structum[®].²⁰⁹⁻²¹²

In a randomized placebo-controlled study of subjects with femorotibial osteoarthritis, dietary supplementation with mixed chondroitin sulfates (1000 mg/day; unknown source) for 3 months produced significantly greater decreases in the Lequesne Index of functional impairment and the severity of pain at rest assessed using a visual analog scale.²¹³ No significant differences occurred in the severity of pain with activity assessed by use of a visual analog scale or in the incidence or severity of side effects. Among the previously-supplemented subjects, pain had not returned three months after discontinuation of supplementation. In a randomized placebo-controlled study of subjects with severe

osteoarthritis of the proximal interphalangeal joints, dietary supplementation with mixed chondroitin sulfates (800 mg/day; unknown source) for 2 years produced significantly greater decreases in the depth of erosions of the femoral articular surface and in the number of painful joints per subject.²¹⁴

Subjects with severe osteoarthritis of the proximal interphalangeal joints received dietary supplementation with Chondral[®] (a polydisperse mixture of chondroitin sulfates; Societa Prodotti Antibiotici, Milan, Italy; 800 mg/day) either with or without naproxen (500 mg/day).²¹⁵ After 2 years, the combination of Chondral[®] and naproxen produced significantly slower progression of cartilage erosions, but the progression of clinical osteoarthritis was not arrested.

Several groups of investigators have applied the techniques of meta-analysis to evaluate dietary supplementation with chondroitin sulfates. One group concluded that 7 randomized double-blind placebo-controlled studies were of adequate quality to include in their analysis.²¹⁶ These studies demonstrated that when consumed at 1200 mg daily for at least 120 days, dietary supplementation with chondroitin sulfates produced significantly greater reductions in the Lequesne Index of functional impairment and in the severity of pain assessed using a visual analog scale than did placebo (the effect size was “large”).²¹⁶ In addition, 65% of subjects consuming chondroitin sulfates will be expected to benefit more than if they were consuming placebo and, in general, adverse effects were more frequent when placebo was consumed than when chondroitin sulfates were consumed.²¹⁶ Other investigators concluded that dietary supplementation with chondroitin sulfates by individuals with osteoarthritis consistently produced significant decreases in joint pain and significant increases in joint function of small-to-moderate magnitude¹⁸⁹ and that dietary supplementation with chondroitin sulfates is “probably effective in osteoarthritis in reducing pain and in improving joint function.”¹⁰⁷

When only “high quality” studies were considered by another investigator, it was concluded that dietary supplementation with chondroitin sulfates by individuals with osteoarthritis produced an approximately 50% reduction in pain with a similar improvement in function (a “large” effect consistently greater than that of placebo).¹⁹¹ However, it was noted that the quality of most published studies concerning dietary supplementation with chondroitin sulfates by individuals with osteoarthritis has been generally poor and that the magnitude of the reported effects of dietary supplementation with chondroitin sulfates are likely to be inflated by weaknesses in the study designs and analysis. Nonetheless, it was concluded that, despite their flaws, the available published studies demonstrate a significant degree of efficacy for dietary supplementation with chondroitin sulfates.¹⁹¹

The application of a pharmacokinetic-pharmacodynamic model of intake-dependent effects resulted in the estimation that dietary supplementation with chondroitin sulfates (especially Condrosulf[®], 1200 mg/day) “can reduce baseline pain and algofunctional

indices by over 80%"; it was estimated that about half of this benefit can be experienced in about 35 days of supplementation.²¹⁷

Comparison of Supplemental D-Glucosamine and Chondroitin Sulfate

In an open-label trial, subjects with femorotibial osteoarthritis consumed either D-glucosamine sulfate (unknown source; 1500 mg/day) or mixed chondroitin sulfates (unknown source; 675 mg/day).²¹⁸ After 3 months there were no significant differences between the two groups of subjects; 72% of all subjects self-assessed their improvement as "good" without side effects. The extent of improvement in pain during moderate exercise following supplementation was inversely proportional to the severity of pain during moderate exercise prior to the initiation of supplementation (subjects with the most severe pain responded the least to either dietary supplement).

Combination of Chondroitin Sulfate and D-Glucosamine in an Animal Model of Osteoarthritis

In a rabbit surgical model of osteoarthritis, following surgery five groups of rabbits were fed either a control diet or the control diet supplemented with either D-glucosamine HCl, mixed chondroitin sulfates, manganese ascorbate or Cosamin[®] for 16 weeks.²¹⁹ Upon sacrifice, the rabbits fed either the control diet or the control diet supplemented with either D-glucosamine HCl, mixed chondroitin sulfates, or manganese ascorbate exhibited no significant differences in the area of articular cartilage surface lesions, the percentage of animals exhibiting severe lesions, the rates of synthesis or degradation of articular cartilage proteoglycans or the magnitude of IL-1 β -induced collagenase activity. In contrast, dietary supplementation with Cosamin[®] produced significantly greater decreases in the area of articular cartilage surface lesions, the percentage of animals exhibiting severe lesions and the magnitude of IL-1 β -induced collagenase activity. In this model, Cosamin[®] had no effect on the rates of synthesis or degradation of articular cartilage proteoglycans.

Combinations of Chondroitin Sulfate and D-Glucosamine and Osteoarthritis

In a randomized double-blind placebo-controlled clinical trial, subjects with mild to moderate femorotibial osteoarthritis supplemented their diets with either a combination of D-glucosamine-HCl (1000 mg/day), mixed chondroitin sulfates (800 mg/day) and manganese ascorbate (152 mg/day) (2 tablets of Cosamin[®]; Nutramax Laboratories, Inc.) or placebo.²²⁰ After 6 months, dietary supplementation with Cosamin[®] was associated with significantly greater decreases in the Lequesne index of functional impairment, although there was no difference in WOMAC pain scores or in subject self-assessment between subjects supplemented with Cosamin[®] and those supplemented with placebo. In addition, subjects with severe femorotibial osteoarthritis experienced little improvement.

There also was no difference in the incidence or severity of side effects. In another randomized double-blind placebo-controlled clinical trial, subjects with mild to moderate femorotibial osteoarthritis or osteoarthritis of the lower back supplemented their diets with either a combination of D-glucosamine-HCl (1500 mg/day), mixed chondroitin sulfates (1200 mg/day) and manganese ascorbate (228 mg/day) (3 tablets of Cosamin[®]; Nutramax Laboratories, Inc.) or placebo.²²¹ After 16 weeks, Cosamin[®]-supplemented subjects with femorotibial osteoarthritis exhibited significantly greater decreases in summary disease score, subject self-assessment of pain, severity of pain assessed using a visual analog scale, but there was no difference in maximum running times. Subjects with osteoarthritis of the lower back exhibited no response to the dietary supplement. There were no intergroup differences in the incidence or severity of side effects.

In a randomized double-blind placebo-controlled trial, dietary supplementation with D-glucosamine-HCl (1500 mg/day) plus mixed chondroitin sulfates (1200 mg/day) was compared with placebo in subjects with painful osteoarthritis of the temporomandibular joint.²²² After 12 weeks, subjects supplemented with D-glucosamine-HCl plus mixed chondroitin sulfates exhibited significantly greater decreases in temporomandibular joint tenderness and sounds and in voluntary consumption of pain relieving medications without the production of side effects. In an uncontrolled study of subjects with chronic temporomandibular joint osteoarthritis, 80% of subjects reported self-perceived decreases in temporomandibular joint sounds during dietary supplementation with a combination of D-glucosamine-HCl (1600 mg/day), mixed chondroitin 4- and 6-sulfates (1200 mg/day) and calcium ascorbate (1000 mg/day) (NOW Foods, Glendale Heights, IL).²²³

Daily Intake of Supplemental Glucosamine that is Effective in Reducing the Risk of Osteoarthritis

The reliable and credible scientific literature indicates that daily dietary supplementation with 1500 mg of D-glucosamine sulfate is effective in reducing the risk of osteoarthritis.

When combined with dietary supplementation with chondroitin sulfates (at least 800 mg/day), daily dietary supplementation with 1000 mg of D-glucosamine-HCl is effective in reducing the risk of osteoarthritis.

Daily Intake of Supplemental Chondroitin Sulfate that is Effective in Reducing the Risk of Osteoarthritis

The reliable and credible scientific literature indicates that daily dietary supplementation with 1200 mg of chondroitin sulfate (containing chondroitin 4-sulfate and chondroitin 6-sulfate in approximately equal proportions), whether consumed alone or in combination with supplemental D-glucosamine sulfate or D-glucosamine-HCl is effective in reducing the risk of osteoarthritis.

Safety of Daily Intakes of Supplemental Chondroitin Sulfate and D-Glucosamine that are Effective in Reducing the Risk of Osteoarthritis

D-Glucosamine is present in all foods containing cartilage or glycoproteins.¹⁷ It has not been possible to estimate an LD₅₀ for oral D-glucosamine sulfate because no deaths have occurred in mice and rats from intakes of up to 5000 mg/kg body weight.²²⁴ Daily dietary supplementation with 2149 mg of D-glucosamine sulfate per kg body weight produced no systemic or gastrointestinal adverse reactions in dogs.¹⁴¹ Horses fed 8 g of D-glucosamine-HCl daily for 48 weeks (equivalent to about 16 mg/kg body weight daily in an adult human) exhibited no effects on bone metabolism.²²⁵ In humans, intra-articular (200 mg)²²⁶ or intramuscular injection of D-glucosamine sulfate (200 mg once²²⁶ or 400 mg daily for 7 days^{227,228}) produced no adverse reactions. Dietary supplementation with D-glucosamine sulfate¹⁷⁶⁻¹⁸¹ or D-glucosamine-HCl^{173-175,220-222} for up to 3 years did not produce an increase in the incidence or severity of side effects in placebo-controlled human studies.

The most common side effects reported by humans consuming D-glucosamine sulfate include reversible epigastric pain, epigastric tenderness, heartburn, nausea, diarrhea, dyspepsia, vomiting, constipation, drowsiness, headaches, and mild skin reactions.^{182,185} Oral D-glucosamine sulfate does not interfere with the efficacy of medications for cardiovascular, liver, or lung diseases, diabetes or depression²²⁷ or produce insulin resistance in rats²²⁹ or humans.^{181,230} However, oral D-glucosamine sulfate may potentiate active peptic ulcers.¹⁸² Obesity may reduce responsiveness to dietary supplementation with D-glucosamine sulfate.¹⁸²

In rats and rabbits, oral chondroitin sulfate polymers (1 g/kg body weight daily) produced no effects on mutagenesis or reproductive function.⁵ In the isolated rabbit intestinal loop model of the digestive tract, no change in the amplitude of intestinal contractions or in the tonicity of the intestine was noted in the presence of 1 to 3 mg/mL chondroitin sulfate polymers. At intakes of 0.25 to 1.0 g/kg body weight, no change occurred in the rate of intestinal transit in mice. Chondroitin sulfate polymers do not modify the coagulation time. Intravenous chondroitin sulfate polymers (25 to 100 mg/kg body weight, perfused at a rate of 25 mg/min) had no effect on the human electrocardiogram; 100 mg/kg induced a slight and transitory decrease of arterial pressure. However, chondroitin sulfate polymers can cause an increased respiratory rate and amplitude. No change in the volume or the electrolyte concentration of human urine was found after subcutaneous administration of 100 mg/mL of chondroitin sulfate polymers.⁵

In an analysis of 16 human studies that included a total of 372 subjects, it was concluded that dietary supplementation with chondroitin sulfate polymers (800 mg/day) did not produce more adverse events than did placebo.²³¹ Dietary supplementation with chondroitin sulfate polymers for up to 2 years did not increase the incidence or severity of side effects in placebo-controlled human studies.^{192-198,202,203,205-207,212-214,220-222}

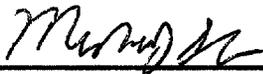
Conclusions

- Maintaining the structural and functional integrity of the proteoglycan component of the extracellular matrix of articular cartilage is required for preservation of healthy joint architecture and biomechanics.
- Imbalanced metabolism favoring catabolism within the extracellular matrix of articular cartilage produces degenerative changes in the proteoglycan composition of the matrix.
- Compromise of the structural and functional integrity of the proteoglycan component of the extracellular matrix of articular cartilage results in net loss of articular cartilage tissue, inferior biomechanical competence and structural deformation of joint architecture.
- Net degradation of the extracellular matrix of articular cartilage, accompanied by the production of spontaneous repair matrix with abnormal proteoglycan composition, results in asymptomatic subclinical osteoarthritic change.
- The progression of asymptomatic osteoarthritic change to osteoarthritis is not inevitable.
- The progression of osteoarthritic change is required in order for abnormalities in articular cartilage composition and structure to progress to osteoarthritis.
- Osteoarthritic change in the absence of joint pain represents a modifiable risk factor for later development of osteoarthritis.
- Dietary supplementation with D-glucosamine, glucosamine-HCl, glucosamine sulfate or chondroitin sulfate contributes to the preservation of articular cartilage, inhibits the initiation of osteoarthritic change in articular cartilage and inhibits the progression of osteoarthritic change to symptomatic osteoarthritis.
- Dietary supplementation with D-glucosamine, glucosamine-HCl, glucosamine sulfate or chondroitin sulfate is an effective modifier of osteoarthritic change and reduces the risk for osteoarthritis.

Summary Conclusions

In conclusion, I find that there is significant scientific agreement in support of the following health claims:

- Glucosamine may reduce the risk of osteoarthritis.
- Chondroitin sulfate may reduce the risk of osteoarthritis.
- Glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis.
- Glucosamine may reduce the risk of osteoarthritis-related joint pain, tenderness and swelling.
- Chondroitin sulfate may reduce the risk of osteoarthritis-related joint pain, tenderness and swelling.
- Glucosamine and chondroitin sulfate may reduce the risk of osteoarthritis-related joint pain, tenderness and swelling.
- Glucosamine may reduce the risk of joint degeneration.
- Chondroitin sulfate may reduce the risk of joint degeneration.
- Glucosamine and chondroitin sulfate may reduce the risk of joint degeneration,
- Glucosamine may reduce the risk of cartilage deterioration.
- Chondroitin sulfate may reduce the risk of cartilage deterioration.
- Glucosamine and chondroitin sulfate may reduce the risk of cartilage deterioration.



Michael J. Glade, Ph.D., F.A.C.N., C.N.S.
(a copy of my CV is attached)

**RMJ Consulting, Inc.
Russell Jaffe, MD, Ph.D., NACB
FASCP, FACN, FACAAI**

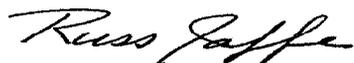
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I, Russell Jaffe, M.D., Ph.D., have read the foregoing scientific report of Dr. Michael John Glade and I concur with its analysis and conclusions in their entirety.



Russell Jaffe (electronic signature)



May 27, 2003

Claudia A. Lewis-Eng
Principal
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To Whom It May Concern:

I, Luke Bucci, Ph.D., have read the foregoing scientific report of Dr. Michael John Glade and I concur with its analysis and conclusions in their entirety.

Sincerely,

A handwritten signature in black ink, appearing to read 'L. Bucci', written in a cursive style.

Luke Bucci, Ph.D.
Vice President Research

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Licensed Dietitian (L.D.), State of Illinois	1995 to present
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EXPERIENCE:

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Senior Research Analyst , ECRI, Plymouth Meeting, PA	1997 to 1998
Senior Scientist , American Medical Association, Chicago, IL	1990 to 1997
Visiting Scientist/Research Assistant Professor Northwestern University, Chicago, IL	1986 to 2002
Assistant Professor , University of Maryland, College Park, MD	1981 to 1986
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Member, Advisory Board Society for Integrative Medicine National Graves' Disease Foundation	1998 to present 1992 to 2001
Recorder Nutrition Sciences Education and Research Fund	1997 to present
Designated Representative of the C.B.N.S. Intersociety Physician Nutrition Education Consortium	1996 to present
Policy Paper Reviewer Council for Agricultural Science and Technology (CAST).	1996 to present
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Part-Time Faculty Biostatistics, University of Bridgeport, Bridgeport, Connecticut	1993 to present
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Book Review Editor <i>Nutrition: The International Journal of Applied and Basic Nutritional Sciences</i>	1992 to present
Manuscript Reviewer <i>The Journal of the American Medical Association, The Journal of the American College of Nutrition, Nutrition, and other peer-reviewed journals</i>	1980 to present
Council Coordinator American College of Nutrition	1994 to 1998
Certification Board for Nutrition Specialists Director Director of Educational Programs President Vice-President Editor, Certifying Examination, Certification Board for Nutrition Specialists Editor/Author <i>1996 Study Guide for the Certifying Examination for Certified Nutrition Specialists</i> <i>1996 Candidate's Guide for Licensure as a Nutrition Counselor, State of Illinois</i> <i>1999 Study Guide for the Certifying Examination for Certified Nutrition Specialists</i> <i>Study Guide for the Certifying Examination for Certified Nutrition Specialists, 3rd Edition</i> Lecturer, "Fundamentals of Human Nutrition" Review Course	1992 to present 2001 to present 1996 to 1999 1992 to 1996 1992 to 2001 1996 1996 1999 2002 2002 to present

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- educational/promotional materials
- seminars and symposia
- publications
- labeling
- regulatory affairs
- scientific product support
- policy development
- research protocol evaluation
- research design/implementation
- data analysis and interpretation
- product formulation

Product formulation and development projects have emphasized the rational combination of select vitamins, minerals, herbs, and phytonutrients and phytomedicines into formulas for individuals who are attempting to quit smoking or who are afflicted with alcoholism, caffeine dependency, colorectal cancer, breast cancer, cardiovascular disease, osteoporosis, arthritis or celiac disease. These projects have included the assembly of scientific substantiation for both product ingredients and product labeling.

Consulting Clinical Nutritionist
North Shore Wellness and Cosmetic Surgery
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September 1999 to present

Patient care in the areas of nutritional support for cancer management, restoration of intestinal function, diabetes, chronic fatigue, multiple sclerosis, mental illness, skeletal function, heart disease, chronic fatigue syndrome, fibromyalgia, morbid obesity, yeast infection and smoking cessation.

Nutritionist/Medical Advisor
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September 2000 to present

Past consulting projects:

Identification and substantiation of structure/function statements for dietary supplements containing ginseng (prepared for a commercial client).

Substantiation of new health claims for dietary supplements containing folic acid (prepared for a petition submitted to the FDA).

Substantiation of new health claims for dietary supplements containing antioxidant vitamins (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing selenium (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing antioxidant vitamins (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing selenium (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing phosphatidylserine (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing glucosamine (prepared for petitions submitted to the FDA).

Substantiation of new health claims for dietary supplements containing chondroitin sulfate (prepared for petitions submitted to the FDA).

Design of human trials to demonstrate the safety of a new dietary ingredient (prepared for a commercial client).

Preparation of the scientific background for petitions to FDA requesting approval to import new dietary ingredients (prepared for commercial clients).

Comparison of scientific manuscripts in several copyright infringement cases.

Substantiation of structure/function statements made for several dietary supplements (prepared for commercial clients).

Data analysis for the development of normal reference intervals for a series of new diagnostic tests.

Scientific substantiation and validation of a survey instrument for the assessment of overall health.

Scientific substantiation of a dietary supplement formulation for the support of cognitive functions (prepared for a commercial client).

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Evaluation of the safety and effectiveness of a dietary supplement formulation for the chelation of heavy metals (prepared for a commercial client).

Evaluation of the safety and effectiveness of a dietary supplement formulation for enlargement of the human female breast (prepared for a commercial client).

Evaluation of the safety and effectiveness of dietary supplement formulations for enhancement of weight loss (prepared for commercial clients).

Evaluation of the safety and effectiveness of dietary supplement formulations for enhancement of sexual function (prepared for a commercial client).

Evaluation of the safety and effectiveness of dietary supplement formulations for enhancement of immune function (prepared for a commercial client).

Evaluation of the safety and effectiveness of dietary supplement formulations for enhancement of sleep (prepared for a commercial client).

Evaluation of the safety and effectiveness of a dietary supplement formulation for reduction of serum total cholesterol concentration (prepared for a commercial client).

Consultations with the Deputy Commissioner of the Food and Drug Administration concerning the scientific substantiation of proposed health claims for dietary supplements.

Presentations since May 1998:

Herbal management of diabetes. Natural Pharmacy East, Arlington, VA, October 1998.

Nutritional support for breaking nicotine addiction. International College for Advancement of Longevity Medicine Fall Symposium, Reno, NV, October, 1998.

Nutritional support for breaking nicotine addiction. Sixth International Congress of the American Academy of Anti-Aging Medicine, Las Vegas, NV, December, 1998.

Nutritional support for breaking nicotine addiction: A randomized, double-blind, placebo-controlled evaluation of a proprietary dietary supplement. American College of Nutrition Annual Symposium, Washington, DC, October, 1999

Efficacy of an enzyme product derived from *Aspergillus niger* and bromelain (AbsorbAid™) in improving protein absorption in nursing home patients on tube feeding. American College of Nutrition Annual Symposium, Las Vegas, NV, October, 2000.

Preventing cancer with nutrition. Prevention Plus, Oak Park, IL, October, 2000.

Celiac disease. Healthy Eating Seminar Series, Lake County Chapter, Celiac-Sprue Association, Waukegan, IL, October, 2000.

Gluten sensitivity and other digestive disorders. Healthy Eating Seminar Series, Lake County Chapter, Celiac-Sprue Association, Deerfield, IL, January, 2001.

Digestive disease; celiac disease; digestive ecology; using diagnostic technology to target trace elements and vitamin therapy. American Naprapathic Association, Countryside, IL, April 22, 2001.

Biomarkers of aging. Chicagoland Anti-Aging Conference, Wilmette, IL, May 19, 2001.

Restoration of digestive ecology. Designs for Health – Advanced Training in Clinical Nutrition, Designs for Health Institute, Boulder, CO, June 30, 2001.

The relationship between digestive tract function and autism. In-service training, Pfeiffer Foundation, Naperville, IL, July 2001.

Nutrition and brain function. Amer, Naprapathic Assoc., Countryside, IL, April 7, 2002.

Fundamentals of Human Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College for the Advancement of Medicine, Ft. Lauderdale, FL, May 15-16, 2002.

Fundamentals of Human Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College of Nutrition, San Antonio, TX, October 2-3, 2002.

Fundamentals of Human Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College of Nutrition, New York, NY. April 5-6, 2003.

Fundamentals of Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College of Nutrition, Miami, FL, April 23-24, 2003.

Michael J. Glade, Ph.D.

Upcoming Presentations:

Fundamentals of Human Nutrition. Two-day Review Course in preparation for the certifying examination of the Certification Board for Nutrition Specialists. American College of Nutrition, New York, NY. April 5-6, 2003.

Teaching Lecture Topics since May 1998:

Environmental medicine and detoxification therapy.
Carbohydrate nutrition and nutritional therapy.
Protein nutrition and nutritional therapy.
Nutritional and herbal management of diabetes.
Nutritional therapeutics in cancer.
Nutrition and cancer prevention for consumers.
Celiac disease and its prevention and treatment.
Free radical and antioxidant biology.
Biostatistics for nutritionists (I designed and am teaching this course both in-class and over the internet)

Michael J. Glade, Ph.D.

ECRI

5200 Butler Pike, Plymouth Meeting, PA 19462

August 1997 to May 1998

**SENIOR RESEARCH ANALYST
Technology Assessment**

Evaluation of medical, nutritional, and technological therapies and diagnostic techniques for human endocrine, metabolic, musculoskeletal, and nutritional diseases.

Quality Assurance Manager, National Guidelines Clearinghouse (with AHCPH)

Participant in database design, National Guidelines Clearinghouse (with AHCPH)

Statistical expert, diagnostic technologies and meta-analysis

Provide in-house expertise to ECRI Management on food, device, drug, agriculture and nutrition-related health, policy, legal, and regulatory matters.

SUPERVISOR: Charles Turkelson, Ph.D.
Chief Research Analyst
Technology Assessment
ECRI

AMERICAN MEDICAL ASSOCIATION

515 N. State St. Chicago, IL 60610

1993 to 1997

SENIOR SCIENTIST, Technology Assessment & Nutrition Department of Technology Assessment

Evaluation of medical, nutritional, and technological therapies and diagnostic techniques for human endocrine, metabolic, musculoskeletal, and nutritional diseases.

Development of Technology Assessments for the AMA *Diagnostic and Therapeutic Technology Assessment (DATTA)* project:

Diagnostic Value of Plasma Lp(a) Concentrations

Diagnostic Value of Plasma Apolipoproteins

Diagnostic Value of Serum Thyroid-Stimulating Hormone (TSH)

Diagnostic Value of Computerized Dynamic Posturography

Diagnostic Value of 24-hour Esophageal pH Monitoring

Therapeutic Value of Peripheral Parenteral Nutrition

Therapeutic Value of Intraoperative Radiotherapy

Therapeutic Value of Speech Therapy in Otitis Media

Therapeutic Value of Recombinant Human Growth Hormone (rhGH) in Children with Short Stature

Therapeutic Value of Mononuclear Leukocyte ("Buffy Coat") Infusions in Chronic Myelocytic Leukemia

Therapeutic Value of Medicinal Leeches

Therapeutic Value of Pedicle Screw Spinal Fixation Systems

Therapeutic Value of Recombinant Human Growth Hormone (rhGH) in Children with Gonadal Dysgenesis

Related Duties:

Statistician; perform statistical analyses for all physician surveys administered by the *DATTA* project.

Co-Editor of the monthly AMA newsletter, *Technology News*.

Provide in-house expertise to AMA Senior Management on food, device, drug, agriculture and nutrition-related health, policy, legal, and regulatory matters.

Secretary, AMA House of Delegates Reference Committee E (advise AMA policy committees on medicine, nutrition, and public health).

Michael J. Glade, Ph.D.

Publications:

Published In:	No. of Publications:
DATTA Assessments:	13
peer-reviewed journals:	4
Proceedings chapters:	4
book reviews:	11
general public press:	16
peer-reviewed journals (submitted):	5

Original articles published in the monthly AMA newsletter, *Technology News*:

Risk Assessment in the Establishment of Upper Safe Limits for Nutrient Intakes	12/96
Dietary Fat and Cancer: Molecular Mechanisms	10/96
Clinical Significance of Melatonin (with B. Kendler)	9/96
Designing, Testing, and Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities	6/96
Dietary Phytochemicals in Cancer Prevention and Treatment	11/95
Electromagnetic Compatibility for Medical Devices: Issues and Solutions	9/95
FDA/NIH-Sponsored Conference: Comparing Treatments: Safety, Effectiveness, and Cost-Effectiveness	5/95
Clinical Significance of Oxidative Stress (with B. Kendler)	11/95
Diet and Cancer: Molecular Mechanisms of Interactions	1-2/95
Management of Disorders of Cholesterol, Triglyceride, and Lipoprotein Metabolism	11/94
AMA Annual Meeting Update (with S. Kalousdian)	7-8/94
Drug and Device-Induced Disease: Developing a Blueprint for the Future	/94
AMA Interim Meeting Update (with S. Kalousdian)	1-2/94
AMA Annual Meeting Update (with S. Kalousdian)	8/93
Breast Cancer Risk and Diet	1/93

Author of AMA policy statements on nutrition issues:

- food irradiation;
- lipoproteinemia;
- bacterial contamination of meat;
- dietary calcium requirements;
- folic acid supplementation to prevent neural tube defects;
- thiamin supplementation of alcoholic beverages to prevent polyneuropathy;
- neonatal hyponatremia from hypo-osmolar bottled water

Michael J. Glade, Ph.D.

Speaking Invitations:

The Dietary Supplement and Health Education Act of 1994. Annual Meeting of the American College of Nutrition, Washington, DC, October, 1995.

Innovation in clinical nutrition. Harvard University, May 6, 1995.

Environmental medicine. New York Chiropractic College, April 29, 1995.

Environmental medicine. New York Chiropractic College, September 11, 1994.

Additional Responsibilities:

Meeting with representatives of the Food and Drug Administration, the US Department of Agriculture, and other federal agencies concerning:

food, device and drug regulation;

food safety;

direct to consumer advertising of medical therapies.

Collaboration with other AMA staff in the development of scripts for television programs aired on American Medical Television.

Represented AMA on "National Educational Forum on Food Safety Issues."

Book Review Editor, *Nutrition: The International Journal of Applied and Basic Nutritional Sciences*.

Reviewed manuscripts submitted to *the Journal of the American Medical Association*, *the Journal of the American College of Nutrition*, and other peer-reviewed journals.

Reviewed advertisements intended for use in AMA publications.

Policy paper reviewer for the Council for Agricultural Science and Technology (CAST).

Invitations to Chair National Meetings:

Invited to chair and organize a session on "Nutritional Controversies" at the 1996 Annual Meeting of the American College of Nutrition, San Francisco.

Invited to serve as co-chairman of a session of the 1994 Malnutrition and AIDS Symposium, Los Angeles.

Invited to serve as co-chairman of a session of the 1994 Annual Meeting of the American College of Nutrition, Atlanta.

SUPERVISOR: Sona Kalousdian, MD, MPH
Department Director, Department of Technology Assessment
American Medical Association
(773) 384-4915

Michael J. Glade, Ph.D.

AMERICAN MEDICAL ASSOCIATION

515 N. State St. Chicago, IL 60610

1990 to 1993

SENIOR SCIENTIST, Endocrinology, Metabolism & Nutrition Department of Drugs

Evaluation of medical and nutritional therapies and diagnostic techniques for human endocrine, metabolic, musculoskeletal, and nutritional diseases.

Extensive revision of chapters in the Congressionally-recognized compendium of FDA-approved unlabeled drug use and nutritional therapy, *AMA Drug Evaluations*:

Fluid, Electrolyte, and Acid-Base Therapy (pp. 865-880*)

Drugs Used for Urolithiasis (pp. 907-924)

Drugs Used in Adrenocortical Dysfunction (pp. 1017-1036)

Drugs Used in Thyroid Disease (pp. 1037-1062)

Vitamins and Minerals (pp. 2283-2306)

Parenteral and Enteral Nutrition (pp. 2307-2362)

Drugs Used in Obesity (pp. 2439-2454)

Treatment of Disorders of Cholesterol and Lipoprotein Metabolism (pp. 2455-2500)

(* page numbers as in the 1995 edition)

Assistant Secretary, AMA House of Delegates Reference Committee E (advise AMA policy committees during development of policies concerning medicine, nutrition, and public health).

Collaboration with other AMA staff in the development of scripts for television programs aired on American Medical Television

Publications:

Published In:	No. of Publications:
<i>AMA Drug Evaluations</i> Chapters:	8
peer-reviewed journals:	12
Proceedings chapters:	6
book reviews:	1
general public press:	6

Speaking Invitations:

A review of hormonal regulation of cartilage growth in foals. Symposium on Equine Osteochondrosis, Cambridge University, United Kingdom, September, 1992.

Marginal copper deficiency as a cause of defective angiogenesis in chondrodysplasia. Symposium on Equine Osteochondrosis, Cambridge University, United Kingdom, September, 1992.

Michael J. Glade, Ph.D.

Endocrine regulation of equine growth plate chondrocytes. Symposium on Equine Osteochondrosis, Cambridge University, United Kingdom, September, 1992.

Equine osteochondrosis as a manifestation of induced episodic "pseudohypothyroidism." Symposium on Equine Osteochondrosis, Cambridge University, United Kingdom, September, 1992.

Insulin and thyroid hormones influence matrix production by chondrocytes. Seminars in Endocrinology, Northwestern University, Chicago, IL, April 2, 1991.

Additional Responsibilities:

Meetings with representatives of the Food and Drug Administration, the US Department of Agriculture, and other federal agencies concerning:

food, device and drug regulation;

food safety;

direct to consumer advertising of medical therapies

Collaboration with Centers for Disease Control in development of recommendations concerning folic acid and the prevention of neural tube defects (*Morbidity and Mortality Weekly*, August 2, 1991, and September 21, 1992).

Author of AMA policy statement on monosodium glutamate.

Provide in-house expertise to AMA Senior Management on food, device, drug, agriculture and nutrition-related health, policy, legal, and regulatory matters.

Represented AMA on "National Educational Forum on Food Safety Issues".

Book Review Editor, *Nutrition: The International Journal of Applied and Basic Nutritional Sciences*.

Review manuscripts submitted to *the Journal of the American Medical Association*, *the Journal of the American College of Nutrition*, and other peer-reviewed journals.

Review advertisements intended for use in AMA publications.

Coordinator, Council on Endocrinology, Bone, and Minerals; American College of Nutrition.

Advisory Board Member, National Graves' Disease Foundation

SUPERVISOR: Joseph Cranston, Ph.D.
Department Director
Department of Drugs
American Medical Association

Michael J. Glade, Ph.D.

NORTHWESTERN UNIVERSITY

303 E. Chicago Avenue, Chicago, IL 60610

1986 to 1990

RESEARCH ASSISTANT PROFESSOR

Department of Pharmacology

Funded originally as an NIH Senior Fellowship, this position - including both research and teaching - has been continued on a part-time, unpaid basis through the present time as a Visiting Scientist, Department of Molecular Pharmacology and Biological Chemistry

Laboratory and field research; presentation and publication of research findings; fund raising; maintenance of laboratory; practice of safe and proper animal housing and handling; practice of safe handling of hazardous substances.

Concentration on the effects of nutrients, hormones and growth factors on skeletal development and disease.

Guest lectures on pancreatic and thyroid disease and their prevention and medical and nutritional management.

Publications:

Published In:	No. of Publications:
peer-reviewed journals:	11
Proceedings chapters:	8
abstracts:	4
general public press:	98

Speaking Invitations:

Response of arthritic chondrocytes to polysulfated glycosaminoglycans. Skeletal Biology Program, Case Western Reserve University, Cleveland OH, May 14, 1990.

Flora and fauna of Africa and Europe. Department of Pharmacology, Northwestern University, Chicago, IL, February 9, 1989.

Influences of diet and endocrinology on equine developmental orthopedic disease. Department of Animal Sciences, University of Guelph, Ontario, Canada, January 18, 1989.

Diet and growth quality. Equine management class, University of Guelph, Ontario, Canada, January 18, 1989.

Fermentation enhancers. Department of Animal Sciences, University of Guelph, Ontario, Canada, January 17, 1989.

Nitrogen metabolism in the equine. Equine management class, University of Guelph, Ontario, Canada, January 16, 1989.

Michael J. Glade, Ph.D.

Feeding and management of pleasure and show horses. Potomac Horse Club, Silver Spring, MD, October, 1988.

Feeding and management of pleasure and show horses. Potomac Horse Club, Silver Spring, MD, October, 1988.

Homeorrhexis and the growing animal. Biological Sciences Seminar, University College, Dublin, Ireland, October 17, 1988.

Nutrition and developmental disorders of equidae. Department of Zoology, University College, Dublin, Ireland, October 17, 1988.

Nitrogen metabolism in horses. Veterinary College of Ireland, Dublin, Ireland, October 14, 1988.

The role of yeast culture in the nutritional management of young horses. 100th Irish Veterinary Congress, Dublin, Ireland, September 23, 1988.

The role of endocrine factors in equine developmental orthopedic disease. Developmental Orthopedic Disease Panel, American Association of Equine Practitioners Annual Meeting, New Orleans, LA, November 29, 1987.

Diet, chondrodysplasias and animals. Oral Biology Seminar, Northwestern University, Chicago, IL, October 29, 1987.

Effects of yeast culture on nitrogen metabolism in young horses. Alltech Biotechnology Symposium, Lexington, KY, April, 1987.

Bibliometric analysis of research activity in Brazil. Central Intelligence Agency, MacClean, VA, March, 1987.

Bibliometric analysis of research activity in Spain. Ministry of Science and Education, Madrid, Spain, March, 1987.

Cartilage disorders associated with changes in thyroid hormone metabolism. The Chicago Endocrine Society, Chicago, IL, December, 1986.

Dietary causes of osteochondrosis. Pathology Seminar, Northwestern University, Chicago, IL, April, 1986.

Michael J. Glade, Ph.D.

UNIVERSITY OF MARYLAND

College Park, Maryland

1981 to 1986

ASSISTANT PROFESSOR, Department of Animal Sciences
College of Agricultural Sciences

Teaching: (Class, laboratory, barn; lecture, hands-on formats)

Animal Husbandry (nutrition, diet formulation, diseases, management, genetics, physiology, functional morphology)

Animal Training (including principles of animal behavior and their application to training)

Safe Animal Handling (including principles of animal behavior and their application to safe practices in handling animals)

Protein Nutrition (graduate course)

Training:

How to Teach and Supervise Animal Training (undergraduate and graduate students; written materials; videotapes)

Laboratory Techniques (undergraduate and graduate students)

Field Research Techniques (undergraduates and graduates)

Dissertation and Scientific Writing

Grant Proposal Preparation

Research:

Animal Nutrition and Physiology Projects, including several in collaboration with the National Zoo, Washington, DC

Publications:

Published In:	No. of Publications:
peer-reviewed journals:	17
Proceedings chapters:	8
abstracts:	8
general public press:	73

Other projects: (in addition to those documented in publications)

hormone secretion rates in pigs

skeletal growth in monkeys

pharmacokinetics of ivermectin in bullfrogs

growth hormone concentrations in horses and zebras

Michael J. Glade, Ph.D.

Invitation to Chair National Meeting:

Invited to serve as co-chairman of a Non-Ruminant Nutrition session at the 1982 meeting of the American Society of Animal Science, Guelph, Ontario, Canada.

Speaking Invitations:

Quality feed management: tips for proper production and storage. Baltimore Horse Seminar, March, 1985.

Dietary carbohydrate induction of the multiple-messenger, inositol-calmodulin pathway. Animal Sciences Seminar, University of Maryland, February, 1985.

The use of ultrasound to monitor neonatal bone development. Invited seminar, Walter Reed Medical Center, Washington, DC, December, 1984.

Mechanisms of dietary induction of osteochondrosis. Invited seminar, Department of Animal Science, University of Alberta, Edmonton, Canada, August, 1984.

The Use of Self-Supervised Activity to Acquaint College Students with the Teacher-Student Dynamic. 10th International Conference, Improving University Teaching, College Park, MD, July, 1984.

Diagnostic ultrasound - a non-invasive method for examining bone. Pediatric Research Conference, University of Maryland School of Medicine, May, 1984.

Electrical stimulation of bone healing. Alice Deal Science Day, May, 1984.

Non-Traditional feeding practices for the performance horse. Maryland Nutrition Conference, Baltimore, MD, March, 1984.

The use of ultrasound. Nutritional Sciences Colloquium, University of Maryland, February, 1984.

Nutrient-hormone interactions and their impact on growth. Nutritional Sciences Colloquium, University of Maryland, February, 1984.

Feeding horses for a lot less money. Eastern Amateur Arabian Horse Show Circuit Fall Meeting, December, 1983.

Equine nutritional requirements. Baltimore Horse Seminar, November, 1983.

The costs of owning a horse, Maryland Society for the Prevention of Cruelty to Animals Field Day, May, 1983.

Ultrasonic measurement of bone strength. Alice Deal Science Day, April, 1983.

Nutritional manipulation of bone and joint development in growing horses. Maryland Nutrition Conference, Washington, DC, March, 1982.

Developmental origins of growth abnormalities. Animal Sciences Seminar, University of Maryland, October, 1981.

Michael J. Glade, Ph.D.

Additional Responsibilities:

Design of Animal Habitats:

Personally redesigned three multi-acre animal housing facilities, and assisted in their physical renovation

Animal Care:

Collaboration with veterinarians in prophylactic and interventive medical care, including personally:

- administering medications by mouth
- injection (intramuscular; intravenous)
- nasogastric intubation; rectal gavage
- bandaging; suturing
- development of growth plate biopsy procedure for ungulates
- necropsy

Animal Management:

Directly responsible for the management, breeding, and training of up to 120 horses residing at multi-building and multi-site facilities whose activities encompassed teaching, research, breeding, continuing adult education, veterinary care, demonstrations

Supervision of Personnel:

Supervision of up to two dozen permanent and temporary full and part time employees and volunteers engaged in animal husbandry

Record Keeping; Budgets:

Directly responsible for planning, developing, administering, and adhering to expense and revenue budgets, and for extensive and comprehensive record-keeping concerning all facets of a major university equine program

Fund-Raising:

Obtaining funds to support all programs and activities

Sources included federal agencies, state agencies, private foundations, private individuals, corporate entities, animal sales, animal rental

Michael J. Glade, Ph.D.

RUTGERS UNIVERSITY

New Brunswick, NJ

1979 to 1981

ASSISTANT PROFESSOR, Department of Animal Sciences

Teaching: (Class, laboratory, barn; lecture, hands-on formats):

Animal Husbandry (nutrition, diet formulation, diseases, management, genetics, physiology, functional morphology)

Animal Training (including principles of animal behavior and their application to training)

Safe Animal Handling (including principles of animal behavior and their application to safe practices in handling animals)

Training:

Field Research Techniques (undergraduates and graduates)

Grant Proposal Preparation

Research:

Animal Nutrition and Physiology Projects

Publications:

Published In:	No. of Publications:
Proceedings chapters	1
abstracts	1

Speaking Invitations:

Digestive physiology of the horse. Animal Sciences Seminar, University of Maryland, September, 1980.

Similarities between effects of dexamethasone on growing cartilage and osteochondrosis dissecans. Animal Science Seminar, University of California at Davis, April, 1980.

Osteochondrosis dissecans and growth suppression in dexamethasone treated horse foals. American Association of Equine Practitioners Annual Meeting, Miami Beach, December, 1979.

Effects of dexamethasone on calcium metabolism of pony foals. Animal Sciences Seminar, Rutgers University, May, 1979.

Michael J. Glade, Ph.D.

Additional Responsibilities:

Design of Animal Habitats:

Personally redesigned a multi-acre animal housing facility, and assisted in its physical renovation

Animal Care:

Collaboration with veterinarians in prophylactic and interventive medical care, including personally:

- administering medications by mouth
- injection (intramuscular; intravenous)
- nasogastric intubation; rectal gavage
- bandaging; suturing; necropsy

Animal Management:

Directly responsible for the management, breeding, and training of up to 11 horses residing at multi-building and multi-site facilities whose activities encompassed teaching, research, continuing adult education, veterinary care, demonstrations

Supervision of Personnel:

Directly responsible for the supervision of two permanent part time employees and a dozen or so volunteers engaged in animal husbandry

Record Keeping; Budgets:

Directly responsible for planning, developing, administering, and adhering to expense and revenue budgets, and for extensive and comprehensive record-keeping concerning all facets of a major university equine program

Fund-Raising:

Obtaining funds to support all programs and activities

Sources included federal agencies, state agencies, private foundations, private individuals, corporate entities, animal sales, animal rental

Michael J. Glade, Ph.D.

Refereed Journal Articles:

1. Glade, M.J. The effects of gestation, lactation, yeast culture and maternal calcium intake on the mechanical strength of equine bone. *Journal of Equine Veterinary Science*: submitted for publication.
2. Heimbürger, D.C., and the Intersociety Professional Nutrition Education Consortium. 2002. Training and certifying gastroenterologists as Physician Nutrition Specialists. *Journal of Clinical Gastroenterology* 34:505-508.
3. Glade, M.J., D. Kendra and M.V. Kaminski, Jr. 2001. Improvement in protein utilization in nursing-home patients on tube feeding supplemented with an enzyme product derived from *Aspergillus niger* and bromelain. *Nutrition* 17:348-350.
4. Heimbürger, D.C., and the Intersociety Professional Nutrition Education Consortium. 2000. Physician-nutrition-specialist track: If we build it, will they come? *American Journal of Clinical Nutrition* 71:1048-1053.
5. Glade, M.J. 1997. Intake of dietary calcium to reduce the incidence of osteoporosis. *Archives of Family Medicine* 6:491-494.
6. Glade, M.J. 1995. Management of disorders of cholesterol, triglyceride, and lipoprotein metabolism. *Archives of Family Medicine* 4:869-878.
7. Glade, M.J. 1995. Continuous ambulatory esophageal pH monitoring. *Journal of the American Medical Association* 274:662-668.
8. Glade, M.J., Y.S. Kanwar and P.H. Stern. 1994. Insulin and thyroid hormones alter chondrocyte metabolism in cell culture independently and in combination. *Connective Tissue Research* 31:37-44.
9. Glade, M.J. 1993. The effects of gestation, lactation, and maternal calcium intake on the mechanical strength of equine bone. *Journal of the American College of Nutrition* 12:372-377.
10. Glade, M.J. 1992. Effects of *Yucca shidigera* extract on feed utilization by equine weanlings. *Journal of Equine Veterinary Science* 12:93-98.
11. Letcher, J. and M.J. Glade. 1992. Efficacy of ivermectin as an anthelmintic in leopard frogs. *Journal of the American Veterinary Medical Association* 200:537-538.
12. Glade, M.J., Y.S. Kanwar and T.J. Hefley. 1991. Enzymatic isolation of chondrocytes from immature rabbit articular cartilage and their maintenance of phenotypic expression in culture. *Journal of Bone and Mineral Research* 6:217-226.
13. Glade, M.J. 1991. Timed administration of leucine, isoleucine, valine, glutamine, and carnitine to enhance athletic performance. *Equine Athlete* 4:1-10.
14. Glade, M.J. 1991. Effects of dietary yeast culture supplementation of lactating mares on the digestibility and retention of the nutrients delivered to nursing foals via milk. *Journal of Equine Veterinary Science* 11:323-329.

Michael J. Glade, Ph.D.

15. Glade, M.J. 1991. Dietary yeast culture supplementation of mares during late gestation and early lactation. 3. Effects on mare and foal plasma metabolite, amino acid and endocrine profiles. *Journal of Equine Veterinary Science* 11:167-175.
16. Glade, M.J. 1991. Dietary yeast culture supplementation of mares during late gestation and early lactation. 2. Effects on milk production, milk composition, weight gain and linear growth of nursing foals. *Journal of Equine Veterinary Science* 11:89-95.
17. Glade, M.J. 1991. Dietary yeast culture supplementation of mares during late gestation and early lactation. 1. Effects on dietary nutrient digestibilities and fecal nitrogen partitioning. *Journal of Equine Veterinary Science* 11:10-16.
18. Glade, M.J. and M.D. Sist. 1990. Supplemental yeast culture alters the plasma amino acid profiles of nursing and weanling horses. *Journal of Equine Veterinary Science* 10:369-379.
19. Glade, M.J. and N.K. Luba. 1990. Benefits to foals of feeding soybean meal to lactating broodmares. *Journal of Equine Veterinary Science* 10:422-428.
20. Glade, M.J. and M. Campbell-Taylor. 1990. Effects of dietary yeast culture supplementation during the conditioning period on equine exercise physiology. *Journal of Equine Veterinary Science* 10:434-443.
21. Glade, M.J. 1990. Polysulfated glycosaminoglycan (PSGAG) accelerates the synthesis of collagen and glycosaminoglycans by arthritic equine cartilage tissues and chondrocytes. *American Journal of Veterinary Research* 51:779-785.
22. Sist, M.D., Youngblood, M.A., Williams, J.F. and Glade, M.J. 1988. Salivary and serum estrone sulfate levels in pregnant mares. *Journal of Equine Veterinary Science* 8: 164-167.
23. Glade, M.J. and M.D. Sist. 1988. Dietary yeast culture supplementation enhances urea recycling in the equine large intestine. *Nutrition Reports International* 37: 11-19.
24. Wright, L.L., M.J. Glade and J. Gopal. 1987. The use of transmission ultrasonics to assess bone status in the human newborn. *Pediatrics Research* 22:541-544.
25. Glade, M.J. and N.K. Luba. 1987. Serum triiodothyronine and thyroxine concentrations in weanling horses fed carbohydrate by direct gastric infusion. *American Journal of Veterinary Research* 48:578-582.
26. Glade, M.J., N.K. Luba, and H.F. Schryver. 1986. Effects of age and diet on the development of mechanical strength by the cannon bones of young horses. *Journal of Animal Science* 63:1432-1444.
27. Glade, M.J. and L.M. Biesik. 1986. Changes in serum hormone concentrations in weanling horses following gastric infusion of sucrose or casein. *Nutrition Reports International* 33:651-659.
28. Glade, M.J. and L.M. Biesik. 1986. Enhanced nitrogen retention in yearling horses supplemented with yeast culture. *Journal of Animal Science* 62:1633-1640.

Michael J. Glade, Ph.D.

29. Glade, M.J. 1986. Estimation of urine flow rate in weanling and yearling horses. *American Journal of Veterinary Research* 47:2151-2156.
30. Glade, M.J. and T.H. Belling. 1986. A dietary etiology for osteochondrotic cartilage. *Journal of Equine Veterinary Science* 6:151-154.
31. Glade, M.J. 1986. The control of cartilage growth in osteochondrosis. *Journal of Equine Veterinary Science* 6:175-187.
32. Glade, M.J. 1986. "Social Sleeping" among confined horses. *Journal of Equine Veterinary Science* 6:155-157.
33. Glade, M.J. and R.A. Salzman. 1985. Effects of hoof angulation on hoof growth and contraction in the horse. *Journal of Equine Veterinary Science* 5:45-50.
34. Glade, M.J. and T.J. Reimers. 1985. Effects of dietary energy supply on serum thyroxine, tri-iodothyronine and insulin concentrations in young horses. *Journal of Endocrinology* 104:93-98.
35. Glade, M.J., D. Beller, J. Bergen, D. Berry, E. Blonder, J. Bradley, M. Cupelo and J. Dallas. 1985. Dietary protein in excess of requirements inhibits renal calcium and phosphorus reabsorption in young horses. *Nutrition Reports International* 31:649-659.
36. Glade, M.J. 1985. Stimulation of electromagnetic osteogenesis in healthy growing yearlings. *Journal of Equine Veterinary Science* 5:149-153.
37. Glade, M.J. 1985. Overfeeding energy to horses. *Journal of Equine Veterinary Science* 5:95.
38. Glade, M.J., S. Gupta and T.J. Reimers. 1984. Hormonal responses to high and low planes of nutrition in weanling Thoroughbreds. *Journal of Animal Science* 59:658-665.
39. Glade, M.J. and T.H. Belling. 1984. Growth plate cartilage metabolism, morphology and biochemical composition in over- and underfed horses. *Growth* 48:473-482.
40. Glade, M.J. 1984. Feeding innovations for the performance horse. *Journal of Equine Veterinary Science* 4:165-168.
41. Glade, M.J. 1984. "Social sleeping" behavior in young horses. *Equine Practice* 6:10-14.
42. Glade, M.J. 1984. The influence of dietary fiber digestibility on the nitrogen requirements of mature horses. *Journal of Animal Science* 58:638-646.
43. Belling, T.H. and M.J. Glade. 1984. A non-destructive biopsy method allowing the rapid removal of live growth plate cartilage. *Veterinary Medicine/Small Animal Clinician* 79:528-531.
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Abstracts and Proceedings:

1. Glade, M.J., Kendra, D., Kaminsky, M.V., Jr. 2000. Efficacy of an enzyme product derived from *Aspergillus niger* and bromelain (AbsorbAid™) in improving protein absorption in nursing home patients on tube feeding. *Proceedings, Annual Meeting of the American College of Nutrition*, Las Vegas, NV, October.
2. Heimburger, D., and IPNEC. 2000. Training the Physician Nutrition Specialist (PNS). *Proceedings, Annual Meeting of the American College of Nutrition*, Las Vegas, NV, October.
3. Glade, M.J. 1998. Nutritional support for breaking nicotine addiction. *Proceedings, Sixth International Congress on Anti-Aging and Biomedical Technologies* (American Academy of Anti-Aging Medicine), Las Vegas, NV, December, p. unpagued.
4. Glade, M.J. 1998. Nutritional support for breaking nicotine addiction. *Proceedings, International College for Advancement of Longevity Medicine Fall Symposium*, Reno, NV, October, unpagued.
5. Glade, M.J. 1998. Herbal management of diabetes. *Proceedings, Second Annual Natural Pharmacy East Conference*, Arlington, VA, October, unpagued.
6. Glade, M.J., and M.E. Allen. 1996. Assessment of skeletal development in leopard geckos. II. Long bone morphometry and breaking strength. *Proceedings, Ninth Dr. Scholl Nutrition Conference*, Chicago, IL, October, unpagued.
7. Glade, M.J. 1995. The Dietary Supplement and Health Education Act of 1994. *Proceedings, Annual Meeting of the American College of Nutrition*, Washington, DC, October, p. 557.
8. Glade, M.J. 1993. CuSO₄ and chelated copper are bioequivalent when added to the diets of nursing foals. *Proceedings, Annual Meeting of the American College of Nutrition*, Chicago, October, p. 589.
9. Glade, M.J. 1993. CuSO₄ and chelated copper are bioequivalent when added to the culture medium of cartilage tissue and cells. *Proceedings, Annual Meeting of the American College of Nutrition*, Chicago, October, p. 589.
10. Glade, M.J. 1992. Equine osteochondrosis as a manifestation of induced episodic "pseudohypothyroidism." *Proceedings, Symposium on Equine Osteochondrosis*, Cambridge University, United Kingdom, September, p. 44.
11. Glade, M.J. 1992. Endocrine regulation of equine growth plate chondrocytes. *Proceedings, Symposium on Equine Osteochondrosis*, Cambridge University, United Kingdom, September, pp. 42-43.
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13. Glade, M.J. 1992. A review of hormonal regulation of cartilage growth in foals. *Proceedings, Symposium on Equine Osteochondrosis*, Cambridge University, United Kingdom, September, pp. 19-20.
14. Glade, M.J. 1992. The effects of gestation, lactation, and maternal calcium intake on the mechanical strength of equine bone. *Proceedings, Annual Meeting of the American College of Nutrition*, San Diego, October, p. 600.
15. Glade, M.J. 1992. Marginal copper deficiency as a cause of defective angiogenesis in chondrodysplasia. *Proceedings, Annual Meeting of the American College of Nutrition*, San Diego, October, p. 600.
16. Glade, M.J., C. Cahill and M. Campbell. 1989. Effect of exercise on plasma growth hormone concentrations in foals. *Proceedings, Equine Nutrition and Physiology Society*, pp. 63-64.
17. Glade, M.J. 1989. Effects of specific amino acid supplementation on lactic acid production by horses exercised on a treadmill. *Proceedings, Equine Nutrition and Physiology Society*, pp. 244-251.
18. Glade, M.J. 1989. Undergraduates and publishable equine research. *Proceedings, Equine Nutrition and Physiology Society*, pp. 233-235.
19. Glade, M.J. 1989. Supplemental yeast culture alters the plasma amino acid profiles of weanling Quarter horses. *Proceedings, Equine Nutrition and Physiology Society*, pp. 119-123.
20. Campbell, M. and M.J. Glade. 1989. Effects of dietary yeast culture supplementation during the conditioning period on heart rates and lactic acid production by horses exercised on a treadmill. *Proceedings, Equine Nutrition and Physiology Society*, pp. 72-78.
21. Glade, M.J. and P.H. Stern. 1988. Effect of polysulfated glycosaminoglycan (PSGAG) on monolayer cultures of articular chondrocytes. *Journal of Bone and Mineral Research*: 3: Suppl. 1:465.
22. Glade, M.J. 1988. The role of endocrine factors in equine developmental orthopedic disease. *American Association of Equine Practitioners* 33:171-189.
23. Wright, L.L., M.J. Glade and J. Gopal. 1987. Transmission ultrasonics to assess bone status in the human newborn. *Pediatrics Research*: 21:440A.
24. Glade, M.J. and N.K. Luba. 1987. Benefits to foals of feeding soybean meal to lactating broodmares. *Proceedings, Equine Nutrition and Physiology Society*, pp. 593-598.
25. Glade, M.J., T.J. Hefley and P.H. Stern. 1987. A cartilage digestion method maximizing digestion rates and cell yields. *Journal of Bone and Mineral Research*: 2: Suppl. 1: Abstr. 422.
26. Glade, M.J. 1987. The development of mechanical strength in the radius and ulna of the juvenile rhesus monkey. *Journal of Bone and Mineral Research*: 2: Suppl. 1: Abstr. 355.

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27. Glade, M.J. 1987. Cross-sectional geometry of equine metacarpal bones: an initial biomechanical investigation. *Proceedings, Equine Nutrition and Physiology Society*, pp. 537-544.
28. Tutsch, L., M.J. Glade and A.O. Sager. 1985. Long bone growth in the limbs of miniature Hormel-Hanford swine. *Proceedings, Swine in Biomedical Research*, p. 73.
29. Glade, M.J. and L.M. Biesik. 1985. Effects of dietary yeast and urea supplementation of the nitrogen metabolism of yearling Thoroughbreds. *Proceedings, Equine Nutrition and Physiology Society*, pp. 26-31.
30. Glade, M.J. 1985. Electromagnetic induction of increased breaking strength in intact growing equine cannon bones. *Proceedings, Equine Nutrition and Physiology Society*, pp. 118-123.
31. Biesik, L.M., M.J. Glade and E.P. Young. 1985. Post-prandial hormone changes, hepatic T₄-5'-deiodinase activities and the incidence of osteochondrosis in growing swine. *Journal of Animal Science*: 61:Abstr. 101.
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34. Glade, M.J. and N.K. Luba. 1984. Maximum cannon bone breaking strength is not increased by overfeeding young horses. *Journal of Animal Science*: 59:Abstr. 171.
35. Glade, M.J. and T.J. Belling, Jr. 1984. Alterations in the growth mechanism resulting from chronic overfeeding of young horses. *Journal of Animal Science*: 59:A13.
36. Glade, M.J. 1984. Insulin and thyroxine responses to high energy and protein feeding of weanling horses. *Journal of Animal Science*: 59:Abstr. 476.
37. Gupta, S. and M.J. Glade. 1983. Effects of high and low planes of nutrition on the endocrinology of growing horses. *Journal of Animal Science*: 57:(Suppl.) A2.
38. Gupta, S. and M.J. Glade. 1983. Hormonal responses to high and low planes of nutrition in weanling Thoroughbreds. *Proceedings, Equine Nutrition and Physiology Society*, pp. 45-49.
39. Glade, M.J., J.A. Seder and H.F. Schryver. 1983. Use of low frequency ultrasound in the measurement of the bone breaking strengths in live horses. *Proceedings, Equine Nutrition and Physiology Society*, pp. 33-38.
40. Glade, M.J. 1982. Nutriture and performance of racing Thoroughbreds. *Journal of Animal Science*: 55: (Suppl.) 381.
41. Glade, M.J. 1982. Nutritional manipulation of bone and joint development in growing horses. *Proceedings, Maryland Nutrition Conference*, pp. 65-68.

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43. Glade, M.J. and P.I. Bell. 1981. Lower digestive tract fermentation rates and nitrogen utilization in horses. *Proceedings, Equine Nutrition and Physiology Society*, pp. 26-29.
44. Nicoletti, J.M., J.E. Wohlt and M.J. Glade. 1980. Nitrogen utilization by ponies and steers as affected by dietary forage-grain ratios. *Journal of Animal Science*: 51: (Suppl.) 269.
45. Glade, M.J., J.E. Lowe, L. Krook, H.F. Hintz and P. Kenney. 1979. Osteochondrosis dissecans and growth suppression in dexamethasone-treated horse foals. *Proceedings, American Association of Equine Practitioners*: 25:361-365.
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47. Demain, A.L., C. Matteo, M. Glade, A. Tanaka, and J. Piret. 1974. Enzymatic synthesis of useful products. *First Intersectional Congress of the International Association of Microbiological Societies*, Tokyo, Japan.

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EDUCATION

Boston University College of Liberal Arts, A.B., Cum Laude, 1972
Boston University 6-Year Medical Program, M.D., Senior Thesis Honors, 1972
Boston University Division of Medical Sciences, Ph.D., Biochemistry, 1972
Medical Internship, University Hospital, BUMC, Boston, MA 1972-3
Residency, Clinical Pathology, National Institutes of Health, Bethesda, MD 1973-5

BOARD CERTIFICATION

DIPLOMATE, National Board Medical Examiners, 1973
DIPLOMATE, American Board of Pathology (Clinical Pathology), 1975
DIPLOMATE, American Board of Pathology (Chemical Pathology), 1976

APPOINTMENTS

National Institutes of Health Clinical Center, CPD, Bethesda, Maryland 1973-1979
Resident 1973-1975
Senior Staff Physician, Clinical Pathology Department 1975-1979
Fellow, Health Studies Collegium 1979-
Light Foundation (Board of Governors) 1980-1999
Director, Princeton BioCenter 1989-1992

Supplemental Training (Certificate Program)

Pathobiology Conference (Aspen, Colorado) 8/8-17/69
Advanced Course in Electron Microscopy (Prof. Keith Porter & Faculty)
Northeastern University (Boston, MA) 1/8-19/70
Course in Acrylamide Electrophoresis, Gelman Corp. (Boston, MA) 8/9-14/70
Synectics Training Course (Cambridge, MA) 8/9-17/71
American Projective Drawing Institute, (Emanuel Hammer, Ph.D.) 8/8-14/76
Certified Clinical Nutritionist (CCN) 1990-

Medical and Surgical Licenses:

Maryland, New York, California, New Jersey, District of Columbia, and Pennsylvania

BNDD Number: BJ25537390

NRC (Radioisotopes) Users Number: NIH 982, 1973

Patent: 4,035,150 (assigned to D.H.E.W.)

Military Service:

Lieutenant Commander, U.S. Public Health Service 1973-7

Commander, U.S. Public Health Service 1977-9

Resigned 1979

Special Training Programs with Certification

Principal Faculty,

Oriental Medical Strategy in Western Medical Practice, HSC, N.Y, 1980-1985

Selected Awards and Honors:

1999 Distinguished teaching award, Great Lakes College of Clinical Medicine

1995- Who's Who in Medicine and Science; in Business Worldwide (and others)

1992 Norman E. Clarke Sr. Lecture, American College for Advancement in Medicine, Colorado Springs, CO.

1981 Research Committee, Illuminating Engineers Society of North America

1981 YPO 200

1980 Department of Consumer Affairs, State of California, Project Manager, Indoor Environment Quality Study, Sacramento, CA

1979 American Academy of Medical Preventics, National Research Awardee, June 17, Denver, CO

1978 Thanatologic Aspects of Aging: The Well, The Ill, The Family and the Staff, New York, NY

1978 2nd International Symposium on Human Functioning: Distinguished Faculty, Wichita, KA

1975 J.D. Lane Award (U.S.P.H.S.) Junior Investigator, Denver, CO

1971 Exhibitor and Awardee, American Medical Association Annual Meeting, Chicago, IL

1971 SQUIBB Exhibit Award Winner

1970 UTMB-SAMA National Research Forum, First Place, Graduate Student Category

1969 Mead Johnson, "Excellence in Research Award"

1966 Boston University Assembly, Outstanding Service Award

1966 Boston University, "Senior of the Year"

Editorships

1971-2 Associate Editor, The New Physician

1972-3 Senior Associate Editor, The New Physician

Scientific Associations and Memberships

American Academy for the Advancement of Science

New York Academy for the Advancement of Science

American Association of Clinical Chemists

Academy of Clinical and Laboratory Physicians and Scientists

Fellow, National Academy of Clinical Biochemistry

Fellow, American College of Nutrition

Fellow, American College for Allergy, Asthma, and Immunology

Fellow, American Society of Clinical Pathologists

American Public Health Association

Royal Society of Medicine

Clinical Immunology Society

Nutrition for Optimum Health Association

Clinical and Research Interests

Nutritional Immunology

Evoking the Human Healing Response

Treatment protocols for chronic, autoimmune illness

Invited Addresses, Symposium, and Colloquia

Dr. Jaffe has given over 1,000 invited addresses, workshops, symposia, and colloquia.

Dr. Jaffe accepts no more than 50 invitations to present worldwide each year.

Scientific Abstracts:

1. Mechanism of Cross-Linkage Inhibition by Penicillamine, in Texas Reports on Biology and Medicine, Spring, 1971.
2. Aggregation of Platelets by Purified Collagens, FASEB, Atlantic City, N.J., Fed Proc 31:243, 1972.
3. Ascorbic Acid (Vitamin C) Inhibits Occult Blood Detection in Stool, AFRC, Atlantic City, Clinical Research 22:453, 1973.
4. Aggregation of Platelets by Different Collagens, AHA, Dallas, Texas, Circ. Sup 3:289, 1974.
5. Role of Quaternary Structure in Collagen: Platelet Interaction, AFRC, Atlantic City, N.J., Clinical Research 23:276, 1975.

6. Binding of Different Collagens to Human Platelets. Proc. 5th Congress International Society for Thrombosis and Haemostasis, Throm Diath Haemorh 34:332, 1976.
7. Role of Quaternary Structure in Collagen Binding to and Aggregation of Platelets, (with Daniel Deykin), Texas Rep. Biol Med 33:4, 1975, 586.
8. Science and Wellness: The New Medicine, Annals American Public Health Assoc, 104: 4080, 1977.
9. The Effect of Cholesterol Supplementation on the Composition of Phospholipids from Platelets and Erythrocytes of Dogs Fed Diets High in Tallow or Cottonseed Oil, R.E. Pitas, G.J. Nelson, R.M. Jaffe, and R.W. Mahley, American Oil Chemists' Society, St. Louis, Missouri, May, 1978.
10. Oxidized Cholesterol and Atherosclerosis. Common Knowledge. 4:14. Winter 1980, 67-72.
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12. Biochemical indices of vitamin status in response to supplement use. Singh A, Jaffe R, Moses F, Dohoda V, Moran R, Kealey B, and Deuster PA. Am J Clin Nutr 51:523, 1990.

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2. Jaffe, R. Interment of the Internship. The New Physician, November, 1971, 701-711.
3. Jaffe, R. Managing the Drug Abuse Crisis. The New Physician, April, 1972, 218-222.
4. Jaffe, R. Report of the Second National Student Conference on Medical Education. SAMA Press, 1972. 142 p
5. Jaffe, R. Blatti, G. Doerr, E. Drug Information Syllabus I: Cannabis. SAMA Press, 1972 12 p
6. Jaffe, R. Blatti, G. Doerr, E. Drug Information Syllabus II: Hallucinogens. SAMA Press, 1972. 24 p
7. Jaffe, R. Blatti, G. Doerr, E. Drug Information Syllabus III: Stimulants. SAMA Press. 1972. 10 p
8. Jaffe, R. Blatti, G. Doerr, E. Drug Information Syllabus IV: Narcotics. SAMA Press. 1972. 16 p
9. Jaffe, R. Blatti, G. Doerr, E. Drug Information Syllabus V: Sedatives. SAMA Press. 1972. 10 p

10. Jaffe, R. Blatti, G. Doerr, E. Drug Information Syllabus VI: Tranquilizers. SAMA Press, 1973. 5 p
11. Jaffe, R. and Deykin, D. Evidence for the Structural Requirement for the Aggregation of Platelets by Collagen. *J. Clin. Invest.* 1974;53:875-883.
12. Jaffe, R. and Deykin, D. Proceedings: Bindings of Collagen to Platelets. *Thromb. diath. Haemorrh.* 1975;34(1):330-332.
13. Jaffe, R. Kasten, B. MacLowry, K. Young, D. False Negative Occult Blood Tests Caused by Ascorbic Acid. *Ann. Int. Med.* 1975;83:824-826.
14. Jaffe, R. Platelet Interaction with Connective Tissue. In *Physiological Reaction of Blood Platelets* (Gordon, Ed.) Elsevier, 1976, 261-292.
15. Jaffe, R. The Science of Wellness Medicine. Proceedings 2nd International Symposium on Human Functioning. Biosynergetics Institute. Wichita, Kansas, 1978.
16. Jaffe, R., Zierdt, W. An Occult Blood Test Procedure not Subject to Inhibition by Reducing Substances. *J. Lab. Clin. Med.* 1975; 93: 879-886.
17. Pitas, R. Nelson, C. Jaffe, R. Mahley, R. 15,18-Tetracosadienoic Acid Content of Sphingolipids from Platelets and Erythrocytes of Animals Fed Diets High in Saturated or Polyunsaturated Fats. *Lipids.* 1978; 13: 551-556.
18. Spiro, T. Jaffe, R. Holland, P. Alter, H. A Study of Street Heroin Lots for the Presence of the Hepatitis-B Surface Antigen. *Drug and Alcohol Dependence,* 1978; 6: 393-397.
19. Jaffe, R. Lawrence, L. Schmid, A. MacLowry, K. Inhibition by Ascorbic Acid (Vitamin C) of Chemical Detection in Urine. *American Journal of Clinical Pathology,* 1979; 42: 468-470.
20. Jaffe, R. Health in the 80s: Toward Optimum Existence. In *Through the 80s: Thinking Globally and Acting Locally* (Feather, Ed.) World Future Society. Washington, DC, 1980, 356p.
21. Jaffe, R. Continuing Care Service and Wellness Medicine. *Archives of Thanatology.* 1980; 8: 2.
22. Jaffe, R. The House Officer and the Dying Patient, In *Wellness Medicine and the Dying Patient.* Chapter 10. (Kutscher, Ed.) ArnoPress, N.Y., N.Y. 1980.
23. Jaffe, R. Bell, I. Ecological Factors in Learning and Behavioral Disorders. *Osteopathic Physician.* 1980; 47: 25-33.
24. Jaffe, R. Indoor Environmental Quality: Report to The Governor. Dept. of Consumer Affairs, Sacramento, California, 1981, 397 p.
25. Jaffe, R. Gerzoff, S. Directory of Experts in Indoor Pollution. Dept. of Consumer Affairs, Sacramento, California., 1981, 88 p.
26. Jaffe, R. Spohn, R. Clean Your Room: Indoor Environmental Quality and Indoor Pollution. Department of Consumer Affairs, Sacramento, California, 1981, 220p.

27. Jaffe, R. Malathion: Risk, Benefit, Safety, and Biological Chemistry. Health Studies Collegium, Vienna, VA, 1982, 157p.
 28. Jaffe, R. Heptachlor: Risk, Benefit, Safety, and Biological Chemistry. Health Studies Collegium, Vienna, VA, 1983, 99p.
 29. Jaffe, R. Immune Reconstitution Protocol: Testing Bechamp's Hypothesis. Health Studies Collegium, Vienna, VA, 1983, 48p.
 30. Jaffe, R. Risk Analysis and Health Assessment. Health Studies Collegium, 1984, 75.
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 40. Jaffe, R. Yanick, P. (Eds) Clinical Chemistry and Nutrition Guidebook: A Physicians Desk Reference, Lake Ariel, Pa: T&H Press, 1988.
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 42. Jaffe, R. Eosinophilia-Myalgia Syndrome Caused by Contaminated Tryptophan. Intl J Biosocial Med Res, 1989;11(2):181-184.
 43. Jaffe, R. Immune Defense and Repair Systems: Clinical Approaches to Immune Function Testing and Enhancement. Townsend Letter for Doctors Part 1: #79/80, 88-92; Part 2: #81/82, 38-44; Part 3: #83/84, 59-64, 1989.
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46. Jaffe, R. Eosinophilia myalgia syndrome (EMS) Secondary to Contaminated Tryptophan. Clinical Experience. *J Nut Med*, 1991; 2: 195-200.
 47. Jaffe, R. Kreusi, O. The Biochemical Immunology Window: A Molecular View of Psychiatric Case Management. *J App Nut*, 1992; 44: 26-43.
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 49. Deuster, PA and Jaffe R. A Novel Treatment for Fibromyalgia Improves Clinical Outcomes in a Community-Based Study. *J Musculo Pain* 1998; 6: 133-149.
 50. Jaffe R. Autoimmunity: Clinical Relevance of Biological Response Modifiers in Diagnosis, Treatment, and Testing, Part I. *Intl J Integrative Med*, 2000; 2 (2): 16-22.
 51. Jaffe R. Autoimmunity: Clinical Relevance of Biological Response Modifiers in Diagnosis, Treatment, and Cofactor Replacement, Part II. *Intl J Integrative Med*, 2000; 2 (4): 58-65.
 52. Jaffe R, Brown S. Acid-Alkaline Balance And Its Effect on Bone Health. *Intl J Integrative Med*, 2000; 2 (6): 7-18,.
 53. Mehl-Madrona L, Jaffe RM. A computer simulation model to predict outcome in diabetes. Invited paper at the IASTED Conference on Computer Modeling. Innsbruck, Austria, February 20, 2002. Proceedings to be published in 2003.
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University of Texas Ph.D. (Biomedical Sciences) 1983
Graduate School of Magna Cum Laude
Biomedical Sciences
Houston, Texas

Postgraduate Training:

Project Investigator Experimental Radiotherapy Jun 1983 -
University of Texas System Oct 1984
Cancer Center, M.D. Anderson
Hospital & Tumor Institute
Houston, Texas

Academic & Professional Appointments:

Heights Hospital Clinical Lab Assistant Jun-Aug 1972
Houston, Texas

Diagnostic Laboratories Special Chemistry Supervisor 1972-1981
Houston, Texas

Laboratory of Pathology Lab Manager Mar-Jun1981
Houston, Texas

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Experimental Radiotherapy M.D. Anderson Hospital Houston, Texas	Project Investigator	Jun 1983 - Oct 1984
Biotics Research Corporation Stafford, Texas	Research Director	1984-1991
Sports Research Corporation Houston, Texas	Technical Consultant	1985-1991
Chiropractic Rehabilitation Association Ridgefield, Washington	Accredited Instructor	1989-present
InnerPath Nutrition Houston, Texas	Director	1991-present
Houston Community College Houston, Texas	Adjunct Faculty Member	1991-1995
North Harris Montgomery County Community College	Adjunct Faculty Member	1991-1995
Memorial City Medical Center Clinical Laboratory Houston, Texas	Medical Technologist	Aug 1991 - Apr 1992
Bering Care Center Houston, Texas	Staff Nutritionist	Aug 1991 - Apr 1992
SpectraCell Laboratories Houston, Texas	Director of Science & Quality	Apr 1992 - Dec 1995
Weider Nutrition International Salt Lake City, Utah	Vice President of Research	Dec 1995- present

Honors & Awards:

Rosalie B. Hite Memorial Fellowship		1981 - 1982 1982 - 1983
Rosalie B. Hite Memorial Fellowship Merit Award for Outstanding Research		1983
Chiropractic Products	Contributing Editor	1988-1995
Health World	Contributing Editor	1989-1995
Houston Health & Fitness	Contributing Editor	1991-1995
International & American Associations of Clinical Nutritionists (IAACN) Dallas, Texas	X Role Delineation Task Force X Texas State Board X National Certification Exam Writer X Scientific Advisory Board ! CCN of the Year, 1994	1991-present
Clinical Nutrition	Member, Board of Trustees	1991-present

Curriculum Vitae -- Luke R. Bucci, Ph.D., C.C.N., C.(A.S.C.P.), C.N.S. (continued)

Certification Board

United States Olympic Committee Colorado Springs, Colorado	Member, Expert Advisory Panel on Nutritional Supplements	1993
Life College Marietta, Georgia	Adjunct Faculty Member	1994-1997
Journal of Applied Nutrition	Advisory Board Member	1994-present
American College of Nutrition	Certified Nutrition Specialist	1994-present
American College of Addictionology & Compulsive Disorders	Certified Addiction Professional	1995-1997
American Chiropractic Association	Diplomate Course Instructor	1996-present
University of Utah Salt Lake City, Utah	Adjunct Assistant Professor	1997-present
Weider Nutrition International	1999 Employee of the Year	1999

Current Professional Society Memberships:

American College of Nutrition
American College of Sports Medicine
American Society of Clinical Pathologists, Associate Member
American Society of Clinical Pathology, Technologist in Chemistry, Certification #003008
International & American Associations of Clinical Nutritionists
United States Naval Institute

Former Professional Society Memberships:

American Academy of Antiaging Medicine (Scientific Advisory Board member)
American Association for the Advancement of Science
American Association of Clinical Chemists
American Association for Physical Health, Education, Research & Development
American Chemical Society
American Public Health Association
American Running & Fitness Association
International Academy of Nutrition & Preventive Medicine
National Strength & Conditioning Association
New York Academy of Sciences
The Oxygen Society
Sigma Xi

A. Published Books and Book Chapters:

1. Bucci, L.R.: Nutrients as Ergogenic Aids in Sports and Exercise, CRC Press, Boca Raton, 1993. (161 pages, 963 references)
2. Bucci, L.R.: Nutrition Applied to Injury Rehabilitation and Sports Medicine, CRC Press, Boca Raton, 1994. (284 pages, 1382 references)
3. Bucci, L.R.: Nutritional Ergogenic Aids, Chapter 14, in Nutrition in Exercise and Sport, Hickson, J.F. Jr., and I. Wolinsky, Eds., 2nd ed., CRC Press, Boca Raton, 1994, 295-346 (458 refs.).
4. Bucci, L.R.: Nutritional Ergogenic Aids, Chapter 9, in Nutrition in Exercise and Sport, Hickson, J.F. Jr., and I. Wolinsky, Eds., CRC Press, Boca Raton, 1989, 107-184 (766 refs.).
5. Bucci, L.R.: Pain Free. The Definitive Guide to Healing Arthritis, Low-Back Pain, and Sports Injuries

- Through Nutrition and Supplements, The Summit Group, Arlington, 1995.
6. Bucci, L.R.: Introduction, Chapter 1, in Sports Nutrition. Vitamins and Trace Elements, Grandjean, A. and I. Wolinsky, Eds., CRC Press, Boca Raton, 1997, 1-28.
 7. Bucci, L.R.: Dietary Supplements as Ergogenic Aids, Chapter 13 in Nutrition in Exercise and Sport, 3rd ed., Wolinsky, I., Ed., CRC Press, Boca Raton, 1998, 315-368. (460 refs.).
 8. Bucci, L.R.: Healing Arthritis the Natural Way, The Summit Group, Arlington, TX, 1997.
 9. Bucci, L.R.: Somatotropin (Growth Hormone) Release by Oral Amino Acids and Peptides in the Long-Lived, Chapter 5 in Anti-Aging Medical Therapeutics, Klatz, R.M. and Goldman, R., Eds., Health Quest Publications, Marina Del Rey, CA, 1997, pp. 36-49.
 10. Bucci, L.R.: Potential Nutraceutical Stimulation of Growth Hormone Production in the Enhancement of Brain Function and Prevention of Brain Senescence. Chapter 18 in Anti-Aging Medical Therapeutics, Volume 2, Klatz, R.M. and Goldman, R., Eds., Health Quest Publications, Marina Del Rey, CA, 1998, pp. 120-134.
 11. Bucci, L.R., and Unlu, L.M.: Proteins and Amino Acids, Chapter 10 in Energy-Yielding Macronutrients & Energy Metabolism in Sports Nutrition, Driskell, J.A. and Wolinsky, I., Eds., CRC Press, Boca Raton, FL, 2000, 191-212.

B. Patents Granted:

1. Crawford, J.F., Bucci, L.R.: Biochemical analysis of antioxidant function. WO97/48821, December 24, 1997.
2. Bucci, L.R.: Structured glycerols and structured phosphatides. WO 98/28978, July 9, 1998.
3. Crawford, J.F., Bucci, L.R.: Biochemical analysis of antioxidant function of lymphocytes in culture. United States Patent 5,985,665, November 16, 1999.
4. Bucci, L.R.: Compositions and treatments for reducing unwanted side effects associated with long-term administration of androgenic testosterone precursors. United States Patent 6,117,429, September 12, 2000.

B. Published Articles in Refereed Journals:

1. Bucci, L.R., W.A. Brock, and M.L. Meistrich: Distribution and Synthesis of Histone 1 Subfractions During Spermatogenesis in the Rat. Experimental Cell Research, **140**: 111-118, 1982.
2. Holmes, S.D., L.R. Bucci, L.I. Lipshultz, and R.G. Smith: Transferrin Binds Specifically to Pachytene Spermatocytes. Endocrinology, **113**: 1916-1918, 1983.
3. Bucci, L.R., W.A. Brock, I.L. Goldknopf, and M.L. Meistrich: Characterization of High Mobility Group Protein Levels During Spermatogenesis in the Rat. Journal of Biological Chemistry, **256**: 8840-8846, 1984.
4. Bucci, L.R., W.A. Brock, and M.L. Meistrich: High Mobility Group Protein 2 Heterogeneity. Enrichment of a Rapidly Migrating Form in Testis. Biochemical Journal, **229**: 233-240, 1985.
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14. Bucci, L.R.: Glucosamine - A New Potent Nutraceutical for Connective Tissues. American Academy of Osteopathy Journal, **3(2)**: 17,27, 1993.
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E. Technical Journal Publications: (1985-1994)

1. Bucci, L.R.: Sports Performance and Supplementation. Today's Chiropractic, **15(1)**: 19, 1986.
2. Bucci, L.R.: Sports Performance and Supplementation. The Texas Journal of Chiropractic, **3(12)**: 25, 1986.
3. Bucci, L.R.: Anabolic Steroids: Use and Alternatives. California Chiropractic Journal, **11(9)**: 19, 1986.
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5. Bucci, L.R., and G.J. Prosch: The Rheumatoid Disease Foundation: A Cure for Arthritis. Health Freedom News, **March**: 18, 1987.
6. Bucci, L.R., and J.C. Stiles: Sports Injuries and Proteolytic Enzymes. Today's Chiropractic, **16(1)**: 31, 1987.
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40. Bucci, L.R.: A Functional Analytical Technique for Monitoring Nutrient Status and Repletion. 2. Validation. Townsend Letter for Doctors, Aug/Sep, 881-884, 1994.
41. Bucci, L.R.: A Functional Analytical Technique for Monitoring Nutrient Status and Repletion. 3. Clinical Findings and Case Reports. Townsend Letter for Doctors, Oct/Nov, 1994.
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F. Invited Presentations:

AIDS Foundation of Houston	Biological Antioxidants)
American Academy of Anti-Aging Medicine	National Health Federation
American Academy of Environmental Medicine	National Institute of Health Office of Dietary
American Academy of Medical Prevention (now	Supplements Conference on Dietary Supplements
ACAM)	for Physically Active People
American Academy of Orthopedic Medicine	National Nutritional Foods Association (and regional
American Academy of Osteopathy	Affiliates)
American Association of Cancer Research	National Strength & Conditioning Association
American Chiropractic Association Council on Sports	Natural Hygiene Society
Injuries	NMC Home Health Care
American Chiropractic Association Diplomate in	Nutracon
Nutrition Course	Nutraamin (Amsterdam Health Clinic & Educational
American College of Addictionology and Compulsive	facility)
Disorders	Palmer College of Chiropractic Nutrition Symposium
American College for Advancement in Medicine	Palmer College of Chiropractic West (Sports Injury
American College of Sports Medicine	Club)
American Society of Biological Chemists	Parker College of Chiropractic (Main Assembly &
American Society of Cell Biology	Nutrition Club)
American Society of Clinical Nutrition	Pennsylvania Chiropractic Society
Angell Memorial Veterinary Hospital (Boston, MA)	PWA Coalition, Houston Chapter
Auburn University School of Veterinary Medicine	Rheumatoid Disease Foundation
Bering Care Center (an AIDS Day-Care Facility,	Southern Tier Veterinary Medical Society (New York
Houston, Texas)	state)
California Strength & Rehab Clinic	Southwestern Developmental Biology Association
Chiropractic Rehabilitation Association	Southwest Environmental Mutagen Society
Cornell University Veterinary Medicine, East New	Texas A&M University Department of Veterinary
York State	Medicine
Council for Responsible Nutrition	Strategic Research Institute
Curaflex Home Health Care	Texas Back Institute
European Naturopath & Medical Groups	Texas Chiropractic College (Main Assembly, classes,
Florida Chiropractic Association	clinics)
Florida Chiropractic Society	Tree of Life Regional Meetings
Functional Medicine Symposium	Tufts University School of Veterinary Medicine
International & American Associations of Clinical	United States Olympic Committee
Nutritionists	University of Guelph
International Congress on Thymus and Immunity	University of Houston (Physical Education classes)
(Maastricht, Netherlands)	University of Missouri Veterinary Medicine School
International Federation of Body Building	University of Texas Health Science Center at
Home Health Care Companies	Houston
Jinro General Foods, Seoul, Korea	University of Utah
John Bastyr College of Naturopathy (now John	Virginia Tech Veterinary Medicine
Bastyr University)	Washington State Board of Pharmacy
Linus Pauling Institute (Therapeutic Application of	World Research Foundation

Regional medical groups, home health care companies, chiropractic associations and nutrition clubs
Numerous high schools, gyms, health spas, fitness centers, triathlete clubs and bodybuilding contests
TV appearances on local news, national cable news, national network news, international network news