

EXHIBIT 1

Based on my review of the reliable and credible publicly available published peer-reviewed scientific literature regarding calcium nutrition, metabolism, and physiology, their interactions with cardiovascular physiology and reproductive physiology and the disease-preventing properties of dietary calcium in the prevention of essential hypertension, gestational hypertension and pre-eclampsia, I conclude that there is significant scientific agreement in support of the following health claims:

- Calcium may reduce the risk of essential hypertension.
- Calcium may reduce the risk of gestational hypertension.
- Calcium may reduce the risk of pre-eclampsia.

Calcium

I. Intestinal Calcium Absorption and Retention of Ingested Calcium

A. Mechanisms of Calcium Absorption

Calcium in foods occurs as salts or in association with other dietary constituents in the form of complexes of calcium ions. Calcium must be released in a soluble, and probably ionized, form before it can be absorbed (i.e., transferred from the intestinal lumen to the circulatory system). Once in a soluble form, calcium is absorbed by two routes, transcellular and paracellular transport.¹

The saturable, transcellular pathway is a multi-step process, involving the entry of luminal calcium ions across the microvillar membrane into the enterocyte, then movement through the cytosol (i.e., translocation to the basolateral membrane), followed by active extrusion from the enterocyte into the lamina propria and diffusion into the general circulation. The entry of calcium ions across the apical membrane of the enterocyte is favored electrochemically because the concentration of calcium ions within the cell (10^{-7} to 10^{-6} M) is considerably lower than that in the intestinal lumen (10^{-3} M), and the cell is electronegative relative to the intestinal lumen.¹ Therefore, the movement of calcium ions across the apical membrane does not require the expenditure of energy. However, because lipid membranes are impermeable to calcium ions, apical entry must involve the participation of a calcium ion channel or integral membrane transporter residing within the brush border membrane. Evidence suggests that the calcium transport protein, CaT1, may be the putative calcium ion transporter.^{2,3}

The intracellular diffusion of calcium ions is thought to be facilitated by a cytosolic calcium-binding protein, calbindin D_{9K}, whose biosynthesis is dependent on the presence of vitamin D (in the form of 1,25-dihydroxycholecalciferol). Calbindin D_{9K} facilitates the diffusion of calcium ions across the cell by acting as an intracellular calcium ferry or

chaperone. The active extrusion of calcium ions at the basolateral membrane takes place against an electrochemical gradient and is mediated primarily by a calcium-dependent ATPase. While each step in the transcellular movement of calcium ions has a vitamin D-dependent component, the intracellular concentration of active calbindin D_{9K} is believed to be rate-limiting in 1,25-dihydroxycholecalciferol-induced transcellular calcium transport.¹

The paracellular route of calcium absorption involves passive calcium transport through the tight junctions between mucosal cells. Because it does not require a transporter and is driven by the large luminal:serosal calcium concentration gradient, this transport pathway is non-saturable and appears to be independent of nutritional or physiologic regulation (although some limited evidence suggests that it also may respond to 1,25-dihydroxycholecalciferol in an as yet unknown manner).^{1,4}

Most calcium absorption in humans occurs in the lower small intestine, but there is some evidence for a colonic component that may increase total calcium absorption by as much as 10%.⁵ However, the large intestine may represent a site of increased importance for calcium absorption when acidic fermentation takes place. Slightly acidic intracolonic pH increases the efficiency of colonic absorption of calcium.⁶ For example, prebiotics acidify slightly the intracolonic pH (secondary to increased production of short-chain fatty acids as byproducts of increased fermentation) and have been shown to increase the fractional true absorption of ingested calcium in human adolescents, young adults and postmenopausal women.⁶

When dietary calcium is abundant, the paracellular pathway appears to be dominant.⁷ When dietary calcium is limited, the active 1,25-dihydroxycholecalciferol-dependent transcellular pathway increases in importance.⁷ Transmembrane calcium receptors (especially in renal tissues) mediate the conversion of 25-hydroxycholecalciferol to biologically-active 1,25-dihydroxycholecalciferol through regulation of the expression of 25-hydroxycholecalciferol-1 α -hydroxylase and thereby indirectly regulate hormone-mediated up-regulation and down-regulation of calbindin D_{9K} activity in mucosal cells.¹ The beginning of a decline in plasma calcium ion concentration evokes an increase in serum 1,25-dihydroxycholecalciferol concentration, which in turn stimulates increased calbindin D_{9K} biosynthesis in the intestinal mucosa.¹

B. Efficiency of Calcium Absorption

The efficiency of absorption of ingested calcium is inversely proportional to chronic calcium intake. However, this adaptive decrease in the fraction of ingested calcium that does not appear in the feces as calcium intake decreases is not sufficient to offset the decrease in the amount of calcium that is absorbed as a result of a decrease in calcium intake.^{8,9} Regardless of the efficiency of absorption, the amount of calcium that is absorbed is directly proportional to the amount ingested.^{8,9} For example, despite the significantly greater efficiency of absorption when human calcium intake is less than 500

mg/day, the total amount of calcium absorbed from such a low-calcium diet is less than half the amount that is absorbed (even with significantly lower efficiency) from a diet providing 1000 mg/day.^{10,11}

The efficiency of calcium absorption varies throughout the life cycle. It is greatest in infancy, when about 60% of consumed calcium is absorbed,¹² decreases during childhood, and increases again early in adolescence, when about 25% of consumed calcium is absorbed.¹³ The efficiency of calcium absorption remains at about this level into middle adulthood.¹³ As adults age beyond middle adulthood, the efficiency of calcium absorption declines gradually. For example, in postmenopausal women and older men, the efficiency of calcium absorption has been reported to decrease by an average of about 0.2 percentage points annually.^{13,14}

Decreased production of estrogen results in decreased efficiency of calcium absorption in women at any age.^{8,13} For example, the apparent absorption of dietary calcium by premenopausal and perimenopausal women ranges between 17% and 58% and decreases slightly with increasing calcium intake.¹⁵ However, women over 65 years old respond to low calcium intakes with significantly smaller increases in fractional calcium absorption than occur in women 20 to 35 years old consuming the same inadequate amount of calcium.¹⁶ Similarly, amenorrheic young women with hypoestrogenic anorexia nervosa have significantly less efficient calcium absorption than is enjoyed by healthy eumenorrheic young women.¹⁷

Racial differences affect the efficiency of calcium absorption. For example, African American girls exhibit significantly more efficient calcium absorption after menarche than do Caucasian girls.¹⁸ Interestingly, African American adults later exhibit significantly lower rates of bone fractures than do Caucasian adults.^{19,20}

C. Calcium Retention

The retention of ingested calcium within the body reflects the interplay among the amount of calcium consumed, the efficiency of calcium absorption, and urinary excretion of calcium. For example, when a group of healthy adult women reduced their calcium intake from 2000 mg/day to 300 mg/day, although their efficiency of calcium absorption increased significantly, their urinary excretion of calcium decreased significantly, and their efficiency of whole body retention of ingested calcium increased significantly (from 27% to 37%), the overall net result was a significant decrease in the net amount of calcium retained (from 540 mg/day to 111 mg/day).²¹

Amenorrheic young women with anorexia nervosa have significantly greater urinary excretion of calcium than healthy eumenorrheic women; coupled with the reduced absorption efficiency also exhibited by such women, these greater losses produce significantly reduced net calcium retention (evidenced by significantly reduced bone mass).¹⁷ Similarly, in contrast to the generally beneficial effects of moderate exercise on

calcium metabolism and skeletal physiology, exercise-induced amenorrhea also produces significantly decreased net calcium retention (and lower bone mass).^{22,23}

Vegetarian diets produce metabolizable anions (such as acetate and bicarbonate) that may increase renal resorption of filtered calcium, decreasing urinary calcium excretion.^{24,25} Consequently, vegetarians may be more efficient retainers of dietary calcium.

Racial differences may affect the efficiency of calcium resorption in the kidneys. For example, African American children aged 9 to 18 years have exhibited significantly less urinary excretion of calcium than similarly-aged Caucasian children.²⁶ In contrast, it was reported that less calcium was excreted in the urine of African American girls before menarche but that urinary calcium excretion was similar in African American and Caucasian girls after menarche.¹⁸

Data from 181 balance studies subjected to nonlinear regression analysis indicate that maximal calcium retention occurs in men and women when dietary calcium intake is 1200 mg/day.²⁷⁻²⁹ Nonetheless, this level of intake may be inadequate for many individuals. For example, a daily intake of 1300 mg of calcium was insufficient to maximize calcium retention in all members of a group of adolescent females.²⁸

II. Essential Hypertension

Chronic essential hypertension is characterized by increased vascular resistance while cardiac output remains normal and is the most common risk factor for cardiovascular disease in the US. Approximately 50 million adults experienced hypertension in the early 1990's, with greater prevalence among men and African-Americans.³⁰ Nearly 75% of affected individuals fail to adequately control their blood pressure.³¹

Although elevated diastolic blood pressure contributes to risk for cardiovascular disease, a stronger predictor of risk for adverse cardiovascular events and premature death is elevated systolic blood pressure.³² Isolated elevated systolic blood pressure, unaccompanied by elevated diastolic blood pressure, may be a harbinger of doom.³³ Even slight elevation in systolic blood pressure, within the limits of "normotension," is directly correlated with the degree of aortic and coronary calcification and reflects subclinical vascular pathology.³⁴

Nephrosclerosis secondary to hypertension is a common cause of progressive renal disease; essential hypertension, whether characterized by elevation in systolic or diastolic pressures or both, is a major etiologic factor in the pathogenesis of end-stage renal disease,³⁵⁻³⁷ accelerates disease progression^{38,39} and predisposes to renal failure.⁴⁰

Identification of the relationship between dietary calcium and blood pressure originates from observations of an inverse epidemiologic association between the hardness (and

therefore the calcium content) of drinking water and mortality from cardiovascular and cerebrovascular disease.⁴¹⁻⁴⁴

A. “Calcium Paradox” and Blood Pressure Regulation

“Calcium paradox” is a well-established pathophysiological phenomenon characterized by increased chronic influx of calcium ions into cells of the myocardium and vascular smooth muscle during relative calcium deficiency.^{45,46} Sustained increased intracellular calcium ion concentration ($[Ca^{2+}]_i$) triggers the ion’s key second messenger functions and inhibits both ATP synthesis and the activity of the ATP-dependent calcium ion transporters that return calcium ions to the extracellular fluid and the intracellular membrane-bound storage vesicles (endoplasmic reticulum, sarcoplasmic reticulum),^{46,47} further increasing $[Ca^{2+}]_i$.⁴⁸ In addition, $[Ca^{2+}]_i$ -induced stimulation of intracellular phospholipases⁴⁹ and neutral proteases^{50,51} increases the permeability of the plasma membrane to calcium ions.⁴⁵ As the 10,000-fold concentration gradient between the extracellular fluid ($10^{-3} M$) and the intracellular cytosol ($10^{-7} M$) is reduced, the spiral of increasing $[Ca^{2+}]_i$ disrupts cellular metabolism and the regulation of cellular functions, including proliferation, differentiation and apoptosis.^{52,53} In vascular smooth muscle, chronically elevated $[Ca^{2+}]_i$ produces hypercontractility, increased resistance to blood flow (hypertension) and calcification of aortic, coronary and peripheral arterial and arteriolar walls.⁴⁶

It has been suggested that chronically elevated $[Ca^{2+}]_i$ within vascular smooth muscle is driven by chronically elevated serum parathyroid hormone (PTH) concentrations secondary to chronic calcium deficiency (nutritional secondary hyperparathyroidism).⁴⁵ Animal models of hypertension exhibit subclinical hypocalcemia,⁵⁴⁻⁵⁶ significantly elevated serum PTH concentrations,⁵⁵⁻⁵⁸ cellular hyperpermeability to calcium ions⁵⁹ and increased $[Ca^{2+}]_i$ in several tissues.⁵⁹⁻⁶² Furthermore, parathyroidectomy of hyperparathyroid spontaneously hypertensive rats alleviates their hypertension; in contrast, cross-transplantation of parathyroid glands from genetically hyperparathyroid donor rats produced hypertension in previously normotensive parathyroidectomized recipient animals.⁶³ These observations provide further evidence in support of the conclusion that essential hypertension may result from chronic secondary hyperparathyroidism⁴⁴ in response to either chronic mild hypercalciuria caused by a primary renal tubular defect in the efficiency of calcium reabsorption from the renal filtrate (“renal calcium leak”)⁶⁴⁻⁶⁷ or chronic dietary calcium deficiency.^{44,68,69}

Because increased cardiac output to compensate for increased peripheral resistance and normalize blood pressure does not occur in essential hypertension, central regulation of blood pressure also must be affected by calcium status.⁷⁰⁻⁷³ For example, patients with mild hypertension respond to high salt intakes (300 mmol daily) with increased sympathetic nervous activity, which can be significantly attenuated by daily dietary supplementation with 2160 mg of elemental calcium for 7 days.⁷⁴

Increased exposure to PTH has significantly increased the $[Ca^{2+}]_i$ in cultured cardiomyocytes,⁷⁵ erythrocytes,⁷⁶ adipocytes,⁷⁷ hepatocytes,⁷⁸ pancreatic endocrine cells,⁷⁸ osteoblast-like cells,⁷⁹ renal tubular cells,⁸⁰ lymphocytes⁸¹ and platelets.^{58,82} Involvement of increased $[Ca^{2+}]_i$ in the pathogenesis of essential hypertension also is suggested by failure of arterial smooth muscle myofilaments removed from spontaneously hypertensive rats to exhibit increased sensitivity to calcium ions,^{83,84} suggesting that the hypercontractive state of these myofilaments *in vivo* reflects chronically elevated $[Ca^{2+}]_i$ in the vascular smooth muscle of spontaneously hypertensive rats.

Consistent with the hypothesis that increased cardiovascular $[Ca^{2+}]_i$ is involved in the pathogenesis of essential hypertension, daily dietary supplementation with calcium (in amounts approximating 50% to 300% of typical daily intakes) has been found to normalize $[Ca^{2+}]_i$ in both platelets^{57,82} and lymphocytes⁸¹ obtained from supplemented spontaneously hypertensive rats. In addition, arterial smooth muscles harvested from similarly calcium supplemented spontaneously hypertensive rats exhibited significantly increased relaxation responses.^{81,83,85-87} Furthermore, daily dietary supplementation with calcium significantly decreased the systolic blood pressure of spontaneously hypertensive rats *in vivo*.^{57,81,83,86-94} Consistent with these findings, dietary calcium deprivation paradoxically has significantly increased the sensitivity of the pressor response in normotensive rats⁹⁵ and the time to relaxation of stimulated mesenteric arterial beds, in addition to increasing arterial blood pressure, in spontaneously hypertensive rats.^{96,97} On the other hand, daily dietary supplementation with calcium has significantly reduced both systolic and diastolic blood pressures and has prevented salt-loading-induced hypertension in normotensive rats,⁹⁸⁻¹⁰⁰ salt-sensitive Dahl-S rats¹⁰¹ and deoxycorticosterone-salt-sensitive rats.¹⁰²⁻¹⁰⁵ Similarly, increasing daily dietary calcium intake 4-fold prevented deoxycorticosterone-induced hypertension in dogs.¹⁰⁶

Evidence suggests that the link between calcium deficiency, parathyroid gland physiology, elevated cardiovascular $[Ca^{2+}]_i$ and hypertension also occurs in humans. Men and women with essential hypertension exhibit subclinical hypocalcemia,¹⁰⁷⁻¹¹⁹ subclinical or clinically-relevant hypercalciuria^{111,117-126} and significantly elevated serum PTH concentrations.^{111,118,121,125-135} Serum total calcium concentrations have been reported to be significantly inversely correlated with blood pressure¹³⁶ and left ventricular posterior wall thickness¹³⁷ in nonhypertensive elderly individuals with normal pressures. It also has been observed that both systolic and diastolic blood pressures and left ventricular mass are significantly positively correlated with serum PTH concentration in adults.^{110,133-139} Increased left ventricular mass and left ventricular posterior wall thickness are independently predictive of hypertension¹³⁷ and their association with hypocalcemia and elevated serum PTH concentrations reinforces the conclusion that chronically inadequate dietary calcium intake is a causative factor in the etiology of essential hypertension.

Additional evidence favors the conclusion that blood pressure is affected by dietary calcium intake. For example, platelets obtained from hypertensive adults exhibited significantly elevated $[Ca^{2+}]_i$ ^{90,135,140-144} and acute experimental elevations in serum PTH concentration were followed by significantly increased $[Ca^{2+}]_i$ in erythrocytes collected from hypertensive adults.¹⁴⁵ Together with the frequent concordance of clinical primary hyperparathyroidism and hypertension, these findings further support the hypothesis that essential hypertension is marked by chronic hyperparathyroidism secondary to chronically inadequate dietary calcium intake.^{146,147}

B. Dietary Calcium and Blood Pressure in Humans

The results of a number of randomized placebo-controlled clinical trials provide support for the conclusion that dietary supplementation with calcium can contribute to blood pressure control in individuals without hypertension¹⁴⁸⁻¹⁵⁸ as well as in hypertensive men and women.^{148,158-172} In four randomized placebo-controlled clinical trials of men and women without hypertension, daily dietary supplementation with calcium produced significant decreases in both systolic and diastolic blood pressures.¹⁴⁸⁻¹⁵¹ In a randomized placebo-controlled clinical trial of men and women without hypertension, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 12 weeks produced significant decreases in both systolic and diastolic blood pressures.¹⁴⁸ In a randomized placebo-controlled clinical trial of men and women without hypertension, daily dietary supplementation with 1500 mg of calcium (as calcium carbonate) for 56 days produced significant decreases in both systolic and diastolic blood pressures as well as in mean arterial pressure.¹⁴⁹ In a randomized placebo-controlled clinical trial of men without hypertension aged 19 to 52 years, daily dietary supplementation with 1500 mg of calcium (as calcium carbonate) for 12 weeks significantly decreased both systolic and diastolic blood pressures.¹⁵⁰ In a randomized placebo-controlled clinical trial of men and women without hypertension aged 18 to 35 years, daily dietary supplementation with 1000 mg of calcium (as calcium gluconate) for 154 days produced significant decreases in systolic and diastolic blood pressures in women and in diastolic blood pressure in men.¹⁵¹

In four randomized placebo-controlled clinical trials of men and women without hypertension, daily dietary supplementation with calcium produced significant decreases in systolic blood pressures, although diastolic blood pressures were not affected.¹⁵²⁻¹⁵⁵ In a randomized placebo-controlled clinical trial of men and women without hypertension aged 21 to 65 years, daily dietary supplementation with 1150 mg of calcium (as yogurt, cottage cheese and milk products) for 8 weeks produced a significant decrease in systolic blood pressure, although diastolic blood pressure was unaffected.¹⁵² In a randomized placebo-controlled clinical trial of young adult men without hypertension, daily dietary supplementation with 2000 mg of calcium (as calcium gluconate) for 16 weeks produced a significant decrease in systolic blood pressure, although diastolic blood pressure was unaffected.¹⁵³ In a randomized placebo-controlled clinical trial of young adult women

without hypertension aged 19 to 23 years, daily dietary supplementation with 1180 mg of calcium as milk for 42 days produced a significant decrease in systolic blood pressure, although diastolic blood pressure was unaffected.¹⁵⁴ In a randomized placebo-controlled clinical trial of elderly institutionalized Chinese men and women without hypertension, daily dietary supplementation with 800 mg of calcium (as calcium citrate) for 11 weeks produced a significant decrease in systolic blood pressure but had no effect on diastolic blood pressure.¹⁵⁵

In two randomized placebo-controlled clinical trials of men and women without hypertension, daily dietary supplementation with calcium produced significant decreases in diastolic blood pressures, although systolic blood pressures were not affected.¹⁵⁶⁻¹⁵⁷ In a randomized placebo-controlled clinical trial of men and women without hypertension aged 30 to 54 years, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 6 months produced a significant decrease in diastolic blood pressure in white women (but not in men or black women) but had no effect on systolic blood pressure in black or white men or women.¹⁵⁶ In a randomized placebo-controlled clinical trial of men without hypertension aged 19 to 24 years, daily dietary supplementation with 500 mg of calcium (as calcium gluconate or a high-calcium yeast product) for 49 days had no effect on systolic blood pressure but supplementation with the high-calcium yeast product significantly decreased diastolic blood pressure.¹⁵⁷

In a randomized placebo-controlled cross-over clinical trial of 26- to 68-year old men and women with or without hypertension, daily dietary supplementation with 1500 mg of calcium (as calcium carbonate) for 56 days produced significant decreases in mean arterial blood pressure in African-Americans and in subjects (regardless of race) who were shown to be "salt-sensitive" (i.e., respond to acute infusion of NaCl with an increase in mean arterial blood pressure).¹⁵⁸

In eight randomized placebo-controlled clinical trials of men and women with hypertension, daily dietary supplementation with calcium produced significant decreases in both systolic and diastolic blood pressures.^{148,158-164} In a randomized placebo-controlled cross-over clinical trial of hypertensive men and women aged 35 to 74 years, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 8 weeks produced significant decreases in both systolic and diastolic blood pressures.¹⁵⁹ In a randomized placebo-controlled clinical trial of hypertensive men and women, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 12 weeks produced significant decreases in both systolic and diastolic blood pressures.¹⁴⁸ In a randomized placebo-controlled cross-over clinical trial of hypertensive hospitalized men and women aged 65 to 86 years, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 8 weeks produced significant decreases in plasma PTH concentration and in both systolic and diastolic blood pressures.¹⁶⁰ In a randomized placebo-controlled clinical trial of hypertensive men and women, daily dietary supplementation with 2000 mg of calcium (as calcium gluconate) for 16 weeks produced significant decreases in both systolic and diastolic blood pressures.¹⁶¹ In a randomized placebo-controlled cross-over clinical trial of hypertensive young adult, middle-aged and

elderly men and women, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 56 days produced significant decreases in both systolic and diastolic blood pressures.¹⁶² In a randomized placebo-controlled cross-over clinical trial of hypertensive men and women aged 24 to 63 years, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 14 weeks produced significant decreases in both systolic and diastolic blood pressures.¹⁶³ In a randomized placebo-controlled clinical trial of "borderline" hypertensive men and women aged 39 to 67 years, daily dietary supplementation with 2160 mg of calcium (as calcium carbonate) for 7 days prevented significant salt loading-induced increases in both systolic and diastolic blood pressures.¹⁶⁴

In five randomized placebo-controlled clinical trials of men and women with hypertension, daily dietary supplementation with calcium produced significant decreases in systolic blood pressures, although diastolic blood pressures were not affected.¹⁶⁵⁻¹⁶⁹ In a randomized placebo-controlled cross-over clinical trial of hypertensive men and women, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 5 days produced a significant decrease in systolic blood pressure, although diastolic blood pressure was unaffected.¹⁶⁵ In a randomized placebo-controlled clinical trial of hypertensive men and women aged 22 to 56 years, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 8 days produced a significant decrease in supine systolic blood pressure, although diastolic blood pressure was unaffected.¹⁶⁶ In a randomized placebo-controlled cross-over clinical trial of hypertensive men and women aged 24 to 56 years, daily dietary supplementation with 1000 mg of calcium (as calcium gluconate) for 105 days produced a significant decrease in systolic blood pressure, but there was no effect on diastolic blood pressure.¹⁶⁷ In a randomized placebo-controlled cross-over clinical trial of hypertensive men and women between the ages of 30 and 64 years, daily dietary supplementation with 150 to 450 mg of calcium (as part of a dietary manipulation) for 42 days produced a significant decrease in systolic blood pressure.¹⁶⁸ In a randomized placebo-controlled clinical trial of hypertensive women aged 35 to 65 years, daily dietary supplementation with 1500 mg of calcium (as calcium carbonate) for 4 years significantly decreased systolic blood pressure.¹⁶⁹

In three randomized placebo-controlled clinical trials of men and women with hypertension, daily dietary supplementation with calcium produced significant decreases in diastolic blood pressures, although systolic blood pressures were not affected.¹⁷⁰⁻¹⁷² In a randomized placebo-controlled clinical trial of mildly hypertensive men and women, daily dietary supplementation with 800 mg of calcium (as calcium carbonate) for 2 months had no effect on systolic blood pressure but produced a significant decrease in diastolic blood pressure in "salt-sensitive" individuals consuming over 200 mmol of sodium daily.¹⁷⁰ In a randomized placebo-controlled clinical trial of hypertensive men and women aged 16 to 29 years, daily dietary supplementation with 1000 mg of calcium (as calcium citrate) for 84 days produced a significant decrease in diastolic blood pressure but had no effect on systolic blood pressure.¹⁷¹ In a randomized placebo-controlled clinical trial of hypertensive men and women aged 31 to 70 years and with

end-stage renal disease, daily dietary supplementation with 2000 mg of calcium (as calcium carbonate) for 6 months produced a significant decrease in diastolic blood pressure but had no effect on systolic blood pressure.¹⁷²

The results of twelve randomized placebo-controlled clinical trials have demonstrated that dietary supplementation with calcium will not produce hypotension in individuals without hypertension.^{135,148,169,173-182} In several randomized placebo-controlled clinical trials of adult men and women without hypertension, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for up to 3 years had no effect on systolic or diastolic blood pressures.¹⁷³⁻¹⁷⁶ In a randomized placebo-controlled cross-over clinical trial of men and women without hypertension, daily dietary supplementation with 100 to 300 mg of calcium (as part of a dietary manipulation) for 42 days had no effect on systolic or diastolic blood pressures.¹⁷⁷ In a randomized placebo-controlled clinical trial of women without hypertension aged 20 to 23 years, daily dietary supplementation with 1500 mg of calcium (as calcium carbonate) for 42 days had no effect on systolic or diastolic blood pressures.¹⁷⁸ In a randomized placebo-controlled clinical trial of women without hypertension aged 35 to 65 years, daily dietary supplementation with 1500 mg of calcium (as calcium carbonate) for 4 years did not affect systolic or diastolic blood pressures.¹⁶⁹ In a randomized placebo-controlled clinical trial of men and women without hypertension, daily dietary supplementation with 1500 mg of calcium (as part of a dietary manipulation) for 12 weeks failed to produce significant decreases in either systolic and diastolic blood pressures.¹⁴⁸ In a randomized placebo-controlled clinical trial of men and women without hypertension, daily dietary supplementation with 1500 mg of calcium for 8 weeks failed to produce significant decreases in either systolic and diastolic blood pressures, although serum PTH concentration was significantly decreased.¹³⁵ In a nonrandomized placebo-controlled cross-over clinical trial of men and women without hypertension aged 20 to 43 years, daily dietary supplementation with 1600 mg of calcium (as calcium lactate) for 7 days had no effect on systolic or diastolic blood pressures.¹⁷⁹ In a randomized placebo-controlled clinical trial of postmenopausal women without hypertension, daily dietary supplementation with 2000 mg of calcium (as calcium gluconate) for 1 year had no effect on systolic or diastolic blood pressures.¹⁸⁰ In a randomized placebo-controlled clinical trial of men and women with or without hypertension, daily dietary supplementation with 800 mg of calcium (as calcium carbonate) for 56 days had no effect on systolic or diastolic blood pressures.¹⁸¹ In a randomized placebo-controlled clinical trial of women with or without hypertension aged 30 to 74 years, daily dietary supplementation with either 1000 mg or 2000 mg of calcium (as calcium carbonate) for 6 months had no effect on systolic or diastolic blood pressures.¹⁸²

The results of other randomized placebo-controlled clinical trials have suggested that dietary supplementation with calcium may not exhibit pharmacologic hypotensive properties in individuals with hypertension.^{148,183-197} These results emphasize the characteristics that distinguish naturally-occurring nutrients such as calcium from synthetic and artificial pharmacologic agents and suggest that the preventive properties of dietary calcium in the maintenance of normal blood pressure may not be accompanied by

therapeutic (or “treatment”) actions in individuals with hypertension. In a randomized placebo-controlled cross-over clinical trial of hypertensive men and women, daily dietary supplementation with 800 mg of calcium (as calcium carbonate) for 56 days had no effect on systolic or diastolic blood pressures.¹⁸³ In several randomized placebo-controlled clinical trials of hypertensive men and women, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for up to 56 days had no effect on systolic or diastolic blood pressures.^{148,184-188} In a randomized placebo-controlled clinical trial of hypertensive men and women, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for 9 months had no effect on systolic or diastolic blood pressures.^{189,190} In a randomized placebo-controlled cross-over clinical trial of hypertensive men and women aged 30 to 65 years, daily dietary supplementation with 1200 mg of calcium (as calcium carbonate) for 3 months had no effect on systolic or diastolic blood pressures.¹⁹¹ In a randomized placebo-controlled clinical trial of hypertensive men and women aged 18 to 75 years, daily dietary supplementation with 1500 mg of calcium (as calcium carbonate) for 28 days had no effect on systolic or diastolic blood pressures.¹⁹² In a randomized placebo-controlled clinical trial of hypertensive men and women aged 28 to 65 years, daily dietary supplementation with 1600 mg of calcium (as calcium lactate gluconate) for 28 days had no effect on systolic or diastolic blood pressures.¹⁹³ In a randomized placebo-controlled cross-over clinical trial of hypertensive men and women, daily dietary supplementation with 2000 mg of calcium (as calcium gluconate) for 12 weeks had no effect on systolic or diastolic blood pressures.¹⁹⁴ In a randomized placebo-controlled cross-over clinical trial of 46- to 75-year old hypertensive men, daily dietary supplementation with 1515 mg of calcium (as a milk dairy product) for 28 days failed to produce any changes in either systolic or diastolic blood pressures.¹⁹⁵ In a randomized placebo-controlled trial of men and women with untreated mild or borderline hypertension, dietary supplementation with calcium (1000 mg daily) in combination with either potassium (60 mmol daily) or magnesium (360 mg daily) for 6 months had no effect on systolic or diastolic blood pressures.¹⁹⁶ In an uncontrolled study, 4 weeks of daily dietary supplementation with calcium (500 mg) had no effect on blood pressure in patients with primary hyperparathyroidism.¹⁹⁷

In contrast to the results obtained in 50 other randomized placebo-controlled clinical trials, in a trial of 11 hypertensive men and women whose results remain unconfirmed 16 years later, daily dietary supplementation with 1000 mg of calcium (as calcium gluconate) for 14 days produced a significant small increase in diastolic blood pressure, although systolic blood pressure was unaffected.¹⁹⁸

The results of several prospective observational studies provide support for the conclusion that dietary supplementation with calcium can prevent hypertension.¹⁹⁹⁻²⁰⁸ In a study of 30,681 men between the ages of 40 and 75 years, both systolic and diastolic blood pressures were significantly inversely proportional to daily dietary calcium intake.¹⁹⁹ Similarly, in a study of 6496 adult men either without hypertension or with untreated hypertension, both systolic and diastolic blood pressures were significantly inversely proportional to daily dietary calcium intake.²⁰⁰ In a study of 212 adult women,

both systolic and diastolic blood pressures during infancy were significantly inversely proportional to maternal daily dietary calcium intake.²⁰¹ In a 10-year study of 6634 men and women between the ages of 25 and 74 years, 4930 without hypertension at the beginning of the study and 1704 with untreated hypertension at the beginning of the study, the odds of developing hypertension requiring medication were significantly decreased by routine daily consumption of 1600 mg of calcium (OR: 0.73; 95% CI: 0.65, 0.83).²⁰² Similarly, in a prospective observational study of 58,218 women between the ages of 31 and 59 years, women with hypertension with the greatest daily intakes of dietary calcium exhibited significantly lower blood pressure than did women with hypertension with the smallest daily intakes of dietary calcium.²⁰³ In a 6-year prospective observational study of 11,342 adult men at high risk for but without evidence of cardiovascular disease at the beginning of the study, the rate of age-associated increase in systolic blood pressure was significantly inversely proportional to dietary calcium intake.²⁰⁴ In three prospective observational studies of men between the ages of 40 and 59 years, diastolic blood pressure was inversely proportional to dietary calcium intake,²⁰⁵⁻²⁰⁷ although systolic blood pressure was inversely proportional to dietary calcium intake in only one study.²⁰⁷ In a prospective observational study of 41,541 women between the ages of 38 and 63 years at the beginning of the study, diastolic blood pressure was inversely proportional to dietary calcium intake.²⁰⁸

The results of four prospective observational studies demonstrated that dietary supplementation with calcium will not produce hypotension in individuals without hypertension.^{202,203,209,210} In a study of 6634 men and women between the ages of 25 and 74 years, blood pressure was independent of dietary calcium intake among those subjects with normal blood pressure.²⁰² In a study of 58,218 women between the ages of 31 and 59 years, blood pressure was independent of dietary calcium intake among those subjects with normal blood pressure.²⁰³ In a study of 239 peri- and postmenopausal women without hypertension, blood pressure was independent of habitual dietary calcium intake.²⁰⁹ In a study of 1714 middle-aged men with borderline hypertension, blood pressure was independent of habitual dietary calcium intake.²¹⁰

The results of over two dozen retrospective cross-sectional studies provide support for the conclusion that dietary supplementation with calcium can contribute to the maintenance of healthy blood pressure.²¹¹⁻²³⁹ In a study of 161 hypertensive men and 154 men without hypertension, men consuming less than 500 mg of calcium daily had a significantly greater risk for essential hypertension than did men consuming more than 500 mg of calcium daily.²¹¹ In a study of 182 adult men and women with and without hypertension, both diastolic and systolic blood pressures were significantly inversely proportional to daily dietary calcium intake.²¹² In a study of 5305 men and women between the ages of 21 and 74 years, both diastolic and systolic blood pressures were significantly inversely proportional to daily dietary calcium intake in women.²¹³ In a study of 1357 men and women either without hypertension or with untreated hypertension, aged 25 to 74 years, both systolic and diastolic blood pressures were significantly inversely proportional to daily dietary calcium intake; in 210 hypertensive

men and women under antihypertensive medication, diastolic blood pressure was significantly inversely proportional to daily dietary calcium intake.²¹⁴ In a retrospective cross-sectional study of 2291 men and women between the ages of 40 and 65 years, both systolic and diastolic blood pressures were significantly inversely proportional to daily dietary calcium intake.²¹⁵ In a study of 5050 men and women between the ages of 30 and 79 years, diastolic blood pressure was significantly inversely proportional to daily dietary calcium intake in men (but not in women); in a substudy of 541 subjects, both systolic and diastolic blood pressures were significantly inversely proportional to daily dietary calcium intake.²¹⁶ In a study of 182 men and women without hypertension between the ages of 20 and 59 years, both systolic and diastolic blood pressures were significantly inversely proportional to daily dietary calcium intake.²¹⁷ In a study of 7543 men and 8053 women without hypertension between the ages of 25 and 69 years, both systolic and diastolic blood pressures were significantly inversely proportional to daily dietary calcium intake.²¹⁸

In a study of 1790 adult men and women, both diastolic and systolic blood pressures were significantly inversely proportional to daily dietary calcium intake in African-American women.²¹⁹ In a study of 2672 men and women between the ages of 35 and 59 years, systolic blood pressure was significantly inversely proportional to daily dietary calcium intake.²²⁰ In a study of 9553 men and women between the ages of 18 and 74 years, in which data were analyzed by sex and race subgroups, only black men exhibited a significant inverse relationship between systolic blood pressure and daily dietary calcium intake.²²¹ In a study of 3854 men and women between the ages of 25 and 74 years, systolic blood pressure was significantly inversely proportional to daily dietary calcium intake in women aged 55 years and older.²²² In a retrospective cross-sectional study of 2055 men and women between the ages of 25 and 74 years, diastolic blood pressure was significantly inversely proportional to daily dietary calcium intake in women.²²³

In a retrospective cross-sectional study of 8058 men and women between the ages of 25 and 74 years, diastolic blood pressure was significantly inversely proportional to daily dietary calcium intake in men.^{224,225} In a study of 476 men and women between the ages of 20 and 59 years, both systolic and diastolic blood pressures were significantly inversely proportional to daily dietary calcium intake in women.²²⁶ In a study of 5480 men and women between the ages of 40 and 74 years, in which data were analyzed by sex and race subgroups, only black men exhibited a significant inverse relationship between diastolic blood pressure and daily dietary calcium intake.²²⁷

In a retrospective cross-sectional study of 111 men and women either with or without hypertension and over 55 years old, hypertensive subjects consumed significantly less calcium daily.²²⁸ In a study of 976 men and women between the ages of 15 and 64 years, individuals with hypertension with the greatest daily intakes of dietary calcium exhibited significantly lower blood pressure than did individuals with hypertension with the smallest daily intakes of dietary calcium.²²⁹ Similarly, among 364 adult men and women, individuals with hypertension with the greatest daily intakes of dietary calcium

exhibited significantly lower blood pressure than did individuals with hypertension with the smallest daily intakes of dietary calcium.²³⁰ In a study of 7953 men and 9077 women either with or without hypertension and over 20 years old, daily dietary calcium intake greater than 1200 mg attenuated the typical age-associated increase in systolic blood pressure.²³¹

In three retrospective cross-sectional studies of men, both diastolic and systolic blood pressures were significantly inversely proportional to daily dietary calcium intake.²³²⁻²³⁴ These studies examined 419 men over 15 years old,²³² 7932 men between 45 and 64 years old,²³³ and 615 men between 45 and 64 years old.²³⁴ In another study of 1928 men between the ages of 40 and 69 years, only systolic blood pressure was significantly inversely proportional to daily dietary calcium intake.²³⁵

In a retrospective cross-sectional study of 6517 women over 65 years old, both diastolic and systolic blood pressures were significantly inversely proportional to daily dietary calcium intake.²³⁶ In a retrospective cross-sectional study of 222 women between the ages of 55 and 80 years, systolic blood pressure was significantly inversely proportional to daily dietary calcium intake.²³⁷ In a retrospective cross-sectional study of 170 men and 182 women, systolic blood pressure was significantly inversely proportional to daily dietary calcium intake.²³⁸ In a cross-sectional study of regional variations in blood pressure and diet, individuals residing in the southern US were found to have significantly higher mean systolic and mean diastolic blood pressures, and significantly lower mean daily calcium intakes, than individuals residing in the remainder of the country.²³⁹

The results of four retrospective cross-sectional studies failed to provide support for the conclusion that dietary supplementation with calcium can reduce blood pressure; several have included adolescents and adults under 25 years of age.^{237,240-242} Blood pressure was found to be independent of dietary calcium intake in studies of 10,358 men and women between the ages of 18 and 75 years,²⁴⁰ 10,425 men and women between the ages of 18 and 74 years,²⁴¹ 86 women between the ages of 20 and 35 years,²³⁷ and 4354 men and women between the ages of 20 and 59 years.²⁴²

Several of the retrospective cross-sectional studies failing to provide support for the conclusion that dietary supplementation with calcium can prevent hypertension have excluded subjects under 25 years of age.^{179,205,214,215,219,220,222-224,227,243-251} In a study of 8058 men and women between the ages of 25 and 74 years, blood pressure was independent of dietary calcium intake.²²⁴ In a study of 2336 cases of death related to hypertension and 2336 matched control deaths, risk for death from hypertension was independent of the calcium concentration in local drinking water.²⁴³ In a study of 2055 men and women between the ages of 25 and 74 years, systolic blood pressure was independent of dietary calcium intake in men and women and diastolic blood pressure was independent of dietary calcium intake in women.²²³ In a study of 3854 men and

women between the ages of 25 and 74 years, diastolic blood pressure was independent of dietary calcium intake in men and women, systolic blood pressure was independent of dietary calcium intake in men and systolic blood pressure was independent of dietary calcium intake in women aged less than 55 years.²²² In a study of 210 hypertensive men and women treated with medication, systolic blood pressure was unaffected by daily dietary calcium intake.²¹⁴ In a study of 76 men between the ages of 30 and 55 years, blood pressure was independent of daily dietary calcium intake.²⁴⁴ In a study of 5050 men and women between the ages of 30 and 79 years, systolic blood pressure was independent of dietary calcium intake in both men and women.²¹⁵ In a study of 2672 men and women between the ages of 35 and 59 years, diastolic blood pressure was independent of daily dietary calcium intake.²²⁰ In a study of 1976 men between the ages of 40 and 55 years, systolic blood pressure was independent of daily dietary calcium intake.²⁰⁵ In a study of 356 men between the ages of 45 and 49 years, blood pressure was independent of daily dietary calcium intake.²⁴⁵ In a study of 5490 men and women between the ages of 40 and 74 years, both diastolic and systolic blood pressures were independent of daily dietary calcium intake.²²⁷ In a study of 7011 men between the ages of 45 and 64 years, with heavy routine alcohol intakes, blood pressure was independent of daily dietary calcium intake.²⁴⁶

In a study of 199 women between the ages of 46 and 66 years, blood pressure was independent of daily dietary calcium intake.²⁴⁷ In a study of 103 women aged 50 years, blood pressure was independent of daily dietary calcium intake.¹⁷⁹ In a study of 131 men and women between the ages of 60 and 92 years, blood pressure was independent of dietary calcium intake.²⁴⁸ In a study of 255 men and women between the ages of 65 and 79 years, diastolic blood pressure was independent of daily dietary calcium intake.²⁴⁹ In a study of 272 men and women 71 years old, with heavy routine alcohol intakes, blood pressure was independent of dietary calcium intake.²⁵⁰ In a study of 1790 adult men and women, both diastolic and systolic blood pressures were independent of daily dietary calcium intake in African-American men and in non-African-American men and women.²¹⁹ In a study of over 12,000 adult men, blood pressure was independent of daily dietary calcium intake.²⁵¹

The results of two retrospective case-control studies provide support for the conclusion that dietary supplementation with calcium can contribute to maintenance of normal blood pressure.^{252,253} In a retrospective case-control study of 10,372 men and women between the ages of 18 and 74 years, systolic blood pressure was significantly inversely proportional to daily dietary calcium intake in individuals with normal blood pressures and in individuals with hypertension.²⁵² In a study of 90 men and women between the ages of 39 and 42 years, individuals with hypertension reported significantly lower mean daily calcium intake than was reported by adults without hypertension.²⁵³

The results of several randomized placebo-controlled trials on children support the conclusion that daily dietary supplementation with a sufficient amount of calcium can

prevent the development of hypertension.^{254,255} In a randomized placebo-controlled clinical trial of African-American adolescents, daily dietary supplementation with 1500 mg of calcium (as calcium gluconate) for 28 days produced significant decreases in both systolic and diastolic blood pressures.²⁵⁴ In contrast, in a randomized placebo-controlled clinical trial of children, daily dietary supplementation with 600 mg of calcium (as calcium citrate malate) for 12 weeks had no effect on systolic or diastolic blood pressures.²⁵⁵

The results of several observational studies on children also support the conclusion that daily dietary supplementation with calcium can prevent the development of hypertension.²⁵⁶⁻²⁵⁹ In a prospective observational study of 89 children between the ages of 3 and 6 years, both systolic and diastolic blood pressures were significantly inversely proportional to daily dietary calcium intake.²⁵⁶ In a retrospective cross-sectional study of 73 children between the ages of 10 and 18 years, diastolic blood pressure (but not systolic blood pressure) was significantly inversely proportional to daily dietary calcium intake.²⁵⁷ In a retrospective cross-sectional study of 296 white and 236 African-American girls between the ages of 14 and 16 years, diastolic blood pressure (but not systolic blood pressure) was significantly inversely proportional to dietary calcium intake.²⁵⁸ In a retrospective cross-sectional study of 55 preadolescent and adolescent girls, systolic blood pressure was significantly inversely proportional to dietary calcium intake.²⁵⁹

The results of two observational studies on children support the conclusion that daily dietary supplementation with calcium will not produce hypotension in children without hypertension.^{260,261} In a retrospective cross-sectional study of 884 children aged 9 years, blood pressure was independent of dietary calcium intake.²⁶⁰ In another retrospective cross-sectional study of 1109 children between the ages of 14 and 18 years, blood pressure was independent of dietary calcium intake.²⁶¹

The findings of a single retrospective cross-sectional study of 404 adult Pima Indians in Arizona suggested that in that particular and genetically unique population, the odds for hypertension were significantly increased by daily dietary calcium intakes greater than about 900 mg.²⁶²

Daily dietary supplementation with calcium has been effective in reducing blood pressures in uncontrolled studies.²⁶³⁻²⁶⁹ In such a study of hypertensive elderly patients, daily dietary supplementation with 2000 mg of calcium for 8 weeks produced significant decreases in serum PTH concentration and in systolic and diastolic blood pressures.²⁶³ In an uncontrolled study of hypertensive men, daily dietary supplementation with 600 mg of calcium for 12 weeks produced a significant decrease in mean arterial pressure.²⁶⁴ In two uncontrolled studies of hypertensive men, daily dietary supplementation with 1400 mg of calcium for 6 weeks produced significant decreases in serum PTH concentration and in systolic and diastolic blood pressures.^{265,266} In an uncontrolled study of hypertensive adults, daily dietary supplementation with 1000 mg of calcium (as calcium carbonate) for

7 days significantly attenuated increases in both systolic and diastolic blood pressures induced by high salt intakes (225 to 250 mEq daily).²⁶⁷ In two uncontrolled studies of adults with mild to moderate essential hypertension, one week of supplementation with 1000 mg of calcium daily produced significant decreases in end-diastolic volume and IIa-mitral valve opening time and significantly improved myocardial relaxation, atrioventricular net compliance and systemic arterial compliance²⁶⁸ and reduced the lability of blood pressure.²⁶⁹ In one isolated uncontrolled study, 1 month of dietary manipulation that increased daily calcium intake by 100 mg failed to affect blood pressure in patients with mild hypertension.²⁷⁰

One review of the evidence available in 2001 concluded that "Blood pressure is inversely associated with...calcium...[intake]."²⁷¹ One review of the evidence available in 2000 concluded that "In daily clinical practice, when a low-salt diet is indicated, this should be complemented with an oral calcium supplement to obtain the best results."²⁷² Another reviewer has concluded that "The blood pressure-lowering effect of calcium may be of particular benefit to the elderly, people of African origin, and pregnant women."²⁷³ Another reviewer has concluded that "Calcium supplementation appears to reduce blood pressure in both a subpopulation of normotensives and in some hypertensives. The groups which may particularly benefit are hypertensive patients with calcium metabolism deficiencies, a part of the normal population which naturally has an increased calcium demand, and subjects with a typically poor calcium diet...."²⁷⁴

Reviewers of the available epidemiologic data have concluded that "adequate calcium intake...may be associated with a reduced risk of developing hypertension...."²⁷⁵ and that "dietary Ca²⁺ deficiency is associated with human hypertension"²⁷⁶ and that daily calcium intake of at least 1000 mg may be associated with at least a small but significant reduction in the risk of developing hypertension.^{277,278} Over a decade ago a group of reviewers concluded that "dietary calcium supplementation to achieve RDA levels of 800 to 1200 mg daily of elemental calcium may help correct a subtle chronic deficiency of this cation and the accompanying salt induced alterations in calcium homeostasis and blood pressure regulation in salt sensitive persons. This appears to be especially the case among blacks and the elderly who typically consume less calcium than the remainder of the population."^{279,280} Other reviewers concluded that "the usual dietary recommendations made for the prevention of osteoporosis are adequate for BP [blood pressure] lowering."²⁸¹ A review of the NHANES I data demonstrated that ensuring a population-wide intake of at least about 800 to 1000 mg of calcium daily could cut in half the prevalence of clinical hypertension in the US.^{282,283} It has been suggested that daily consumption of at least 800 to 1000 mg of calcium from all sources will confer cardiovascular benefit.²⁸⁴

The results of meta-analyses have concurred. A meta-analysis of randomized placebo-controlled clinical trials that was published in 1989 concluded that in individuals without hypertension, daily dietary supplementation with calcium produced statistically significant reductions in standing systolic and diastolic blood pressures, although supine

systolic and diastolic blood pressures were not significantly affected.²⁸⁵ Similarly, in individuals with hypertension, daily dietary supplementation with calcium produced statistically significant reductions in standing systolic and diastolic blood pressures, although supine systolic and diastolic blood pressures were not significantly affected.²⁸⁵ A meta-analysis of randomized placebo-controlled clinical trials that was published in 1996 concluded that in individuals without hypertension, daily dietary supplementation with calcium produced a statistically significant reduction in systolic blood pressure, although diastolic blood pressure was not significantly affected.²⁸⁶ Similarly, in individuals with hypertension, daily dietary supplementation with calcium produced a statistically significant reduction in systolic blood pressure, although diastolic blood pressure was not significantly affected.²⁸⁶ Another meta-analysis of randomized placebo-controlled clinical trials that was published in 1996 concluded that in individuals with hypertension, daily dietary supplementation with calcium produced statistically significant reductions in systolic and diastolic blood pressures, although supplementation had no effect on the blood pressures of individuals without clinically-apparent hypertension.²⁸⁷ Meta-analyses of randomized placebo-controlled clinical trials that were published in 1998²⁸⁸ and 1999²⁸⁹ concluded that daily dietary supplementation with calcium produced statistically significant reductions in systolic and diastolic blood pressures; individuals with and without clinically-apparent hypertension were not differentiated. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNCVI) recommends increased calcium intake as part of a lifestyle program for the prevention of hypertension.²⁹⁰ In its 2001 Consensus Opinion, the North American Menopause Society stated "Trials have demonstrated that calcium intake is associated with a beneficial effect on hypertension."²⁹¹

III. Gestational Hypertension and Pre-eclampsia

Hypertension is the second most common maternal complication of pregnancy (after anemia), impacting about 10% of all pregnancies.²⁹²⁻²⁹⁴ Gestational hypertension (transient hypertension of pregnancy) accompanies the second half of gestation and even though this disorder usually resolves spontaneously by 12 weeks postpartum, its presence significantly increases the risks for prematurity, intrauterine fetal demise, growth retardation and abruptio placentae and maternal thrombotic microangiopathy and coagulopathy, cerebral hemorrhage and renal and liver damage.^{294,295}

About 25% to 50% of women developing gestational hypertension may progress to more serious pre-eclampsia.^{292,293} Preeclampsia is defined as hypertension and proteinuria beginning during the second half of gestation.²⁹² The combination of pregnancy, hypertension, edema and proteinuria is pathognomonic.²⁹⁶ These core symptoms may be accompanied by hemoconcentration, hypoalbuminemia, abnormal liver function, hypercoagulability, or elevated serum uric acid concentration.²⁹⁶ Other common features of pre-eclampsia include decreased cardiac output, decreased pulmonary capillary wedge

pressure, hypovolemia, increased peripheral vascular resistance and exaggerated pressor responses to vasoconstrictor agents.²⁹⁶ Pre-eclampsia accounts for more than 40% of all premature births worldwide and, following progression to convulsive eclampsia, is the leading cause of maternal death.^{295,297-300} Approximately 5% of previously-normotensive pregnant women and as many as 25% of previously hypertensive pregnant women develop pre-eclampsia.^{292,300}

The etiologies of gestational hypertension and pre-eclampsia are not known. However, in pre-eclampsia, maternal endothelial invasion of the placenta is impaired, resulting in defective decidualization and abnormal subplacental vasculature.²⁹⁴ Abnormal placentation results in elevated resistance to the uteroplacental circulation, producing persistent placental underperfusion, and a general vasoconstrictive state that potentiates peripheral vascular resistance and produces systemic maternal hypertension, reduced organ perfusion, and activation of the coagulation cascade.^{297,301-303} In mid-term of an unaffected pregnancy, peripheral vasodilation, cardiac stroke volume and output, blood volume, renal blood flow and glomerular filtration rate are increased while blood pressure decreases. In contrast, the pre-eclamptic pregnancy exhibits increased peripheral vascular resistance, failure to develop the hypervolemia of pregnancy, reductions in renal blood flow and glomerular filtration rate and increased vascular reactivity to vasoconstrictor agents.³⁰⁴ Pharmacologic control of hypertension during pregnancy significantly improves gestational outcomes, including the needs for preparturient hospitalization or Caesarian delivery.³⁰⁵

A. Dietary Calcium and Gestational Hypertension and Pre-Eclampsia

Although the etiologies of gestational hypertension and pre-eclampsia have not been identified, indirect evidence has led to the suggestion that calcium metabolism may be altered in affected women and that increasing calcium intake may be an effective preventive measure.^{298,306-311} In addition, epidemiologic evidence has indicated that women with gestational hypertension consumed significantly less calcium than did normotensive pregnant women^{312,313} and had significantly lower plasma calcium concentrations³¹⁴⁻³¹⁷ (although not in all studies)²⁹³ and significantly higher serum PTH concentrations.³¹⁵

The results of fourteen randomized placebo-controlled clinical trials provide support for the hypothesis that daily dietary supplementation with calcium may reduce the risk for gestational hypertension.^{316,318-330} In a randomized placebo-controlled clinical trial comparing placebo to daily dietary supplementation with 2000 mg of elemental calcium begun during the second trimester, supplementation reduced the risk for gestational hypertension in all pregnant women by over 80% (OR: 0.07; significantly different from OR = 1.0, $p < 0.05$;^{318,319} OR: 0.11; significantly different from OR = 1.0, $p < 0.05$ ³¹⁶) and in pregnant women at high risk for gestational hypertension (OR: 0.07; significantly different from OR = 1.0, $p < 0.05$ ^{316,318}). In similar studies in which the diet was supplemented with either placebo or 2000 mg of calcium daily, the risk for gestational

hypertension was reduced by over 80% (OR: 0.41; significantly different from OR = 1.0, $p < 0.05$ ³²⁰), by over 70% (OR: 0.28; 95% CI: 0.08, 0.80;³²¹ OR: 0.28; 95% CI: 0.09, 0.84;³²²), by over 50% (OR: 0.46; 95% CI: 0.25, 0.86³²³) and by about 35% (OR: 0.63; 95% CI: 0.44, 0.90³²⁴). In other similar randomized placebo-controlled clinical trials, the risk for gestational hypertension was significantly reduced by daily dietary supplementation with 1000 mg of calcium (OR: 0.22; 95% CI: 0.21, 0.23;³²⁵) or 500 mg of calcium (OR: 0.29; 95% CI: 0.12, 0.46³²⁶). In other placebo-controlled studies, pregnant women whose diets were supplemented with either 375 mg,³²⁷ 1000 mg,³²⁸ 1500 mg³²⁹ or 2000 mg³³⁰ of calcium daily beginning in mid-gestation exhibited significantly lower systolic and diastolic blood pressures than did pregnant women supplemented with placebo.

However, in eight placebo-controlled studies, dietary supplementation with calcium (375 mg daily,³²⁷ 1000 mg daily,^{320,330} 1800 mg daily³³¹ or 2000 mg daily^{299,332,333} beginning in mid-gestation or 600 mg daily from weeks 22 to 32 of gestation and 1200 mg daily from week 32 until parturition³³⁴) failed to affect the risk for gestational hypertension.

The results of six randomized placebo-controlled clinical trials provide support for the hypothesis that daily dietary supplementation with calcium begun during the second trimester may reduce the risk for pre-eclampsia.^{317,321,323,331,333,335} In these trials, supplementation with 2000 mg reduced the risk for pre-eclampsia by about 80% (OR: 0.18; significantly different from OR = 1.0, $p < 0.05$;³¹⁷ RR: 0.13; 95% CI: 0.01, 0.64³²¹ and RR: 0.20; significantly different from OR = 1.0, $p < 0.05$ ³²³). Similarly, supplementation with 1800 mg daily reduced the risk for pre-eclampsia by over 50% (OR: 0.44; 95% CI: 0.21, 0.90).³³¹ In two randomized placebo-controlled clinical trials of women at high risk for pre-eclampsia, daily dietary supplementation with either 600 mg³³⁵ or 2000 mg of calcium³³³ significantly reduced the incidence of pre-eclampsia. However, in six similar studies, dietary supplementation with calcium (375 mg daily,³²⁷ 1500 mg daily³²⁹ or 2000 mg daily^{299,324,330,332}) failed to affect the risk for pre-eclampsia.

The results of a case-control study showed no effect of calcium intake on blood pressure during pregnancy.³³⁶ The authors of one report of a prospective observational study stated that the incidence of pre-eclampsia was not related to daily dietary calcium intake, but provided no data to support this assertion.³³⁷

In a high-profile randomized placebo-controlled clinical trial, women with prestudy daily calcium intakes averaging 1100 mg received no additional preeclampsia preventive benefit from an additional 2000 mg daily.²⁹⁹ However, subgroup analyses revealed that the risk for preeclampsia was significantly reduced by supplementation in adolescents, women with poor calcium consumption, women with pre-existing hypertension and women carrying more than one fetus.²⁹⁸

In 1995 a reviewer declared “Observational studies in pregnant women suggest an inverse association between calcium intake and the incidence of hypertensive disorders of pregnancy...Although it is rather difficult to isolate the effect of calcium intake from the intake of other mineral elements, results from calcium supplementation trials are supportive for calcium being the most important.”³³⁸ A systematic review of 14 published randomized placebo-controlled clinical trials concluded that daily supplementation with 1500 to 2000 mg of calcium during pregnancy significantly reduced maternal systolic and diastolic blood pressures and produced on average a significant 70% reduction in the risk of gestational hypertension and a significant 62% reduction in the risk of preeclampsia.³³⁹ The effect of supplemental calcium was most evident in women with daily calcium intakes of less than 500 mg.³³⁹ This finding was confirmed by another systematic review, which determined that the benefit was most evident in women with daily calcium intakes of less than 900 mg.³⁴⁰ An earlier systematic review had determined that daily supplementation with 1500 to 2000 mg of calcium during pregnancy significantly reduced the risks for gestational hypertension (pooled OR: 0.44; 95% CI: 0.33, 0.59), pre-eclampsia (pooled OR: 0.34; 95% CI: 0.22, 0.54), and preterm delivery (pooled OR: 0.66; 95% CI: 0.45, 0.97).³⁴¹ Another reviewer concluded that “calcium supplements attenuate increases of blood pressure during pregnancy.”²⁷⁴ The authors of the most recently published systematic reviews concluded that “Calcium supplementation to women at high risk of hypertension during pregnancy or low calcium intake reduced the incidence of both preeclampsia and hypertension”³⁴² and “Calcium supplementation appears to be beneficial for women at high risk of gestational hypertension and in communities with low dietary calcium intake.”³⁴³ The Cochrane Collaboration concluded that “Calcium supplementation appears to be beneficial for women at high risk of gestational hypertension and in communities with low dietary calcium intake.”³⁴⁴

IV. Bioavailability of Calcium from the Diet and from Dietary Supplements

Calcium absorption efficiency is fairly similar for most foods, including milk, dairy products and grains.²⁹ However, the efficiency of calcium absorption is reduced when the food sources include spinach, sweet potatoes, rhubarb, beans, unleavened bread, seeds, nuts, or soy isolates.²⁹ The fractional absorption of calcium from dietary supplements typically ranges from 25% to 35% (similar to range for calcium in milk).²⁹ In particular, men and women absorb calcium from calcium citrate and calcium carbonate with equivalent efficiency.^{345,346} However, clinical achlorhydria may impair absorption of calcium from calcium carbonate while enhancing the absorption of calcium from calcium citrate.³⁴⁷

V. Amounts of Supplemental Dietary Calcium that Are Effective in Reducing the Risks of Essential Hypertension, Gestational Hypertension and Pre-Eclampsia

The reliable and credible scientific literature indicates that daily dietary supplementation with calcium-containing compounds in amounts that provide sufficient elemental calcium to allow individuals to achieve daily total calcium intakes consistent with current Institute of Medicine recommendations for gender, age and reproductive status are effective in reducing the risks essential hypertension, gestational hypertension and pre-eclampsia.

Current recommended daily calcium intakes are 800 mg (4 through 8 years old), 1300 mg (9 through 18 years old), 1000 mg (19 through 50 years old) and 1200 mg (over 50 years old).²⁹ These intakes were chosen in order to ensure maximal skeletal development and duration.²⁹ Importantly, it appears that certain health benefits (particularly the antihypertensive property of dietary calcium) occur only at intakes at least equal to the skeletal requirement.

Unfortunately, daily calcium consumption meets or exceeds these amounts in only a small fraction of the population.²⁹ For example, only half of children 4 to 8 years old consume at least 800 mg of calcium daily; less than 25% of boys 9 to 13 years old consume at least 1300 mg of calcium daily; less than 50% of boys 14 to 18 years old consume at least 1300 mg of calcium daily; only about 5% of adolescent girls consume at least 1300 mg of calcium daily; less than 50% of adult men and only about 10% of adult women consume at least 1000 mg of calcium daily; and less than 10% of the population over 50 years old consumes at least 1200 mg of calcium daily.²⁹ Recognizing the limitations of any recommendations that rely solely on the implementation of changes in life-long eating and dietary habits, the Institute of Medicine has suggested that “some seemingly healthy individuals may require higher calcium intakes”³⁴⁸ and that for individuals at risk for dietary calcium intakes below recommendations, “use of calcium supplements may be desirable in order to meet [recommendations].”³⁴⁹

VI. Safety of Dietary Supplementation with Calcium in Amounts that Are Effective in Reducing the Risks of Essential Hypertension, Gestational Hypertension and Pre-Eclampsia

The US Food and Drug Administration has published its finding that the following calcium-containing compounds are “safe”: calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate and calcium sulfate.^{350,351}

The Tolerable Upper Limit of Intake (“the maximal level of nutrient intake that is unlikely to pose risks of adverse health effects to almost individuals in the target group”³⁴⁸) for calcium has been set at 2500 mg daily for males and females over 1 year

of age,²⁹ providing an ample margin of safety for individuals choosing to improve their health by supplementing their diets with calcium. This limit is not set lower during pregnancy or lactation and compares favorably with estimates of daily calcium consumption by modern hunter-gatherers.¹³ The Food and Nutrition Board of the Institute of Medicine has stated that “for the majority of the general population, intakes of calcium from food substantially above the UL are probably safe.”²⁹

No adverse events have occurred when adults with chronic renal failure and receiving hemodialysis have consumed up to 8000 mg of calcium carbonate (providing up to 3200 mg of elemental calcium) daily for up to 48 months^{352,353} or when adults with chronic renal failure and not yet receiving hemodialysis have consumed up to 3000 mg of calcium carbonate (providing up to 1200 mg of elemental calcium) daily for 6 months.³⁵⁴ In these patients, daily dietary supplementation with calcium produced significant improvements in the clinical hyperphosphatemia caused by chronic renal failure.³⁵²⁻³⁵⁴ In addition, both dialyzed³⁵³ and nondialyzed patients³⁵⁴ experienced attenuation of disease-induced secondary hyperparathyroidism and bone resorption. Similarly, adults with chronic renal failure and receiving hemodialysis have consumed an unspecified amount of calcium as calcium acetate for 8 weeks with significant improvements in clinical hyperphosphatemia.³⁵⁵ Boys and girls aged 1 month to 16 years with chronic renal failure and undergoing hemodialysis regularly and consuming 10 to 340 mg of calcium carbonate per kg body weight daily (providing 4 to 136 mg of elemental calcium per kg body weight daily, equivalent to a daily intake of 400 to 13,600 mg of elemental calcium by a 100-kg adult) also have exhibited significantly attenuated hyperphosphatemia and secondary hyperparathyroidism without any adverse reactions.³⁵⁶

Increased risk for the development of symptomatic “milk alkali syndrome” (renal impairment, hypercalcemia, alkalosis) may accompany daily intakes of over 4,000 mg of elemental calcium, particularly if accompanied by equivalently large amounts (over 6,000 mg) of carbonate.³⁵⁷ However, 4 days of daily supplementation with up to 5200 mg of elemental calcium and up to 7800 mg of carbonate was without adverse effect in young adult men and women³⁵⁸ and 4 months of daily supplementation with 3240 mg of carbonate has been without adverse effect in healthy premenopausal women.³⁵⁹ Individuals with uremia, hypothyroidism, adrenocortical insufficiency or PTH-secreting tumors may develop clinically relevant hypercalcemia after routine chronic daily consumption of 4,000 mg or more of elemental calcium.³⁶⁰

One investigator calculated a Lowest Observed Adverse Effect Level (LOAEL) for calcium for individuals with a history of nephrolithiasis of 1685 mg daily, an amount more than current Institute of Medicine recommendations.³⁶¹ The US Food and Drug Administration has concluded that daily intakes of elemental calcium up to at least 1800 mg pose no increased risk for kidney stones among the general population.³⁵¹

A characteristic shared by all of the studies cited in this document is the absolute lack of any reports of any clinically-significant adverse reactions that could be attributed to

dietary calcium. As noted by the North American Menopause Society in their 2001 Consensus Opinion, "The side effect profile from recommended levels of calcium intake is insignificant. No calcium intervention trials have reported any serious side effect associated with these levels."²⁹¹

VII. Additional Literature regarding Relationships between Dietary Supplementation with Calcium and Reduction of the Risks of Essential Hypertension, Gestational Hypertension and Pre-Eclampsia

This literature review is by necessity brief and targeted to the requirements of the US Food and Drug Administration as concerns a balanced presentation of the published peer-reviewed scientific evidence relevant to the proposed health claims. However, it should be noted that the scientific literature upon which this review relies represents only a small fraction of the total available scientific literature base that may be relevant to the relationships between dietary supplementation with calcium, cardiovascular physiology, hypertension and reproductive physiology. Literature searches performed on August 26, 2003, on the following topics obtained these numbers of citations:

Calcium and Hypertension (11851 citations)

Calcium and Safety (1511 citations)

While there is some (undetermined) degree of repetition in the citations identified by these somewhat related searches, clearly there are at least 12000 unique citations that could be construed to be in some way relevant to this review. After examination of the 13362 citations listed above, 361 were found to be germane to the proposed health claims.

Conclusions

- The amount of ingested calcium that is absorbed increases with increasing daily dietary calcium intake.
- Daily dietary calcium intake of at least 1200 mg of elemental calcium is required in order to maximize the retention of absorbed calcium.
- The amount of dietary calcium required daily in order to maximize calcium retention is approximated by the current Institute of Medicine intake recommendations for this nutrient.
- Essential hypertension is associated with chronic secondary hyperparathyroidism.
- Chronic dietary calcium deficiency produces chronic secondary hyperparathyroidism.
- Chronic dietary calcium deficiency is a causative factor in the etiology of essential hypertension.
- The risk for essential hypertension is inversely correlated with daily dietary calcium intake.
- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient contribute to the maintenance of systolic and diastolic blood pressures within their normal ranges.
- Transient hypertension developing during pregnancy (gestational hypertension) increases the risks for fetal, neonatal and maternal complications and death.
- A common characteristic of women who develop gestational hypertension is chronic inadequate intake of dietary calcium producing secondary hyperparathyroidism.
- Daily intakes of calcium that satisfy the current Institute of Medicine intake recommendations for this nutrient contribute to the maintenance of systolic and diastolic blood pressures within their normal ranges during pregnancy.
- Daily intakes of calcium satisfying the current Institute of Medicine intake recommendations for this nutrient reduce the risk for the onset of gestational hypertension.
- Gestational hypertension may progress to pre-eclampsia, a precursor of potentially fatal eclampsia.

- Reducing the risk for gestational hypertension reduces the risk for pre-eclampsia.
- Daily intakes of calcium satisfying the current Institute of Medicine intake recommendations for this nutrient reduce the risk for the progression of gestational hypertension to pre-eclampsia.
- Routine chronic consumption of dietary and supplemental calcium in amounts consistent with the current Institute of Medicine recommendations for this nutrient is safe.

Summary Conclusions

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

- Calcium may reduce the risk of essential hypertension.
- Calcium may reduce the risk of gestational hypertension.
- Calcium may reduce the risk of pre-eclampsia.

/s/ Michael J. Glade¹

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

¹ The original signature page is on file with Emord & Associates, P.C., counsel to Marine Bio Inc. Dr. Glade requested that it not be submitted to FDA to avoid having it posted on the internet and available for nefarious use.

Michael John Glade, Ph.D.

8612 Kedvale Avenue, Skokie IL 60076

TEL: (847)-329-9818

e-mail: the_nutrition_doctor@yahoo.com

EDUCATION:

Ph.D., Animal Science - Nutrition 1979
Cornell University, Ithaca, New York

Bachelor of Science, Molecular Biology 1973
Massachusetts Institute of Technology, Cambridge, Massachusetts

PROFESSIONAL AND CAREER OBJECTIVES:

To contribute to the improvement of public health in the areas of nutrition and public health policy through an internationally recognized nutrition program

LICENSES, CERTIFICATIONS, HONORS:

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

Certified Nutrition Specialist (C.N.S.) 1993 to present

Fellow, American College of Nutrition (F.A.C.N.) 1992 to present

Honorary Member, Irish Veterinary Medical Association 1988 to present

EXPERIENCE:

Independent Consultant May 1998 to present

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

Assistant Professor, Rutgers University, New Brunswick, NJ 1979 to 1981

Director and Nutritionist Adviser to the Board of Directors International College of Advanced Longevity Medicine	1998 to present
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
Lecturer Capital University of Integrative Medicine, Washington, DC New York Chiropractic College (Diplomate in Nutrition program) Northwestern University Medical School, Chicago, IL	1999 to present 1998 to present 1990 to 2002
Part-Time Faculty Biostatistics, University of Bridgeport, Bridgeport, Connecticut	1993 to present
Adjunct Faculty Union Institute, Cincinnati, Ohio	2000 to present
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,</i> and other peer-reviewed journals	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,</i> <i>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

Complete Nutrition Expertise

May 1998 to present

8612 Kedvale Avenue
Skokie IL 60076

- technical support
- 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
281 Waukegan Road, Northfield, IL 60093

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
Lake County Chapter, Celiac-Sprue Association

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).

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.

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).

Publications:

Published In:	No. of Publications:
<i>DATTA</i> 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

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

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.

Homeorrhesis 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.

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

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.

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

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.

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

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.
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