A R T I C L E

Calcium and Disease: Hypertension, organ calcification, & shock, vs. respiratory energy

SOME CONTEXTS
In biology and biochemistry, calcium is the substance most often studied, so it is significant that researchers still speak of a calcium paradox.
There are several such paradoxes: As bones lose calcium, the soft tissues calcify; when less calcium is eaten, blood calcium may increase, along with calcium in many organs and tissues; if an organ such as the heart is deprived of calcium for a short time, its cells lose their ability to respond normally to calcium, and instead they take up a large, toxic amount of calcium.
Magnesium deficiency and calcium deficiency have some similar symptoms (such as cramping), but magnesium is antagonistic to calcium in many systems. It is the basic protective calcium blocker.
Inflammation leads to excessive uptake of calcium by cells, and is a factor in obesity, depression, and the degenerative diseases.
Protein deficiency is an important cause of deranged calcium metabolism. Vitamins K, E, and A are important in regulating calcium metabolism, and preventing osteoporosis. Aspirin (with antiestrogenic and vitamin E-like actions) is protective against bone resorption and hypercalcemia.

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It is extremely important to realize that calcium deposits in soft tissues become worse when the diet is *low in calcium.* Persons suffering from arthritis, bursitis, scleroderma, hardening of the arteries and any abnormality where calcium deposits or spurs may cause pain are often afraid to eat foods rich in calcium. Actually they can never improve until their calcium and magnesium intakes are adequate. Not infrequently physicians tell individuals with kidney stones to avoid all milk, thereby causing stones to form even more rapidly. Such calcium deposits can also occur when vitamin E is undersupplied. After open-heart surgery, when both magnesium and vitamin E are drastically needed and could easily be given, the calcification of heart muscles often becomes so severe that it can cause death within a few days. Pages 171-172, *Lets Eat Right to Keep Fit,* Adelle Davis, Signet, 1970.

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Almost all biologists think of the organism as a machine, regulated by information according to innate programs. When it comes down to the details, their explanations sometimes make Rube Goldbergs imaginary contraptions seem elegant. At their best, they usually rely on some mysterious things called ionic pumps, that perform active transport, powered by little motors, under instructions from molecules that act on their specific receptors. When things get unmanageable, the biologists speak of paradoxes.
Calcium is the most studied of all regulatory molecules, so it isnt surprising that there is more than one calcium paradox. But there are ways of looking at the organism, focusing on energy metabolism, that

dont involve the *ad hoc* theory of calcium pumps, and that make it easy to keep things in context.

Ionized atoms and molecules behave in orderly ways, in relation to their size and their electrical charge. Organic material, even when its dead, selectively binds certain metal ions, and excludes others. The living organism produces a stream of metabolic products, such as carbon dioxide or lactic acid, which interact specifically with each other and with the metal ions, modifying their concentrations inside cells and in the body fluids. This movement of ions can be called active transport, without invoking the mysterious machinery of membrane pumps. Chemical changes produced inside cells, for example by respiration, create different electrical charges in different compartments (inside and outside of capillaries, for example) which affect the movements of water and ions, by simple physical processes, not by molecular pumps.

The result of these passive and active processes is that each kind of ion has a characteristic concentration in each compartment, according to the metabolic energy state of the organism.

Magnesium and potassium are mainly intracellular ions, sodium and calcium are mainly extracellular ions. When cells are excited, stressed, or de-energized, they lose magnesium and potassium, and take up sodium and calcium. The mitochondria can bind a certain amount of calcium during stress, but accumulating calcium can reach a point at which it inactivates the mitochondria, forcing cells to increase their inefficient glycolytic energy production, producing an excess of lactic acid. Abnormal calcification begins in the mitochondria.

When cells are stressed or dying, they take up calcium, which tends to excite the cells at the same time that it inhibits their energy production, intensifying their stress. A cramp or a seizure is an example of uncontrolled cellular excitation. Prolonged excitation and stress contribute to tissue inflammation and fibrosis.

Gross calcification generally follows the fibrosis that is produced by inflammation.

Arteries, kidneys, and other organs calcify during aging. At the age of 90, the amount of calcium in the elastic layer of an artery is about 35 times greater than at the age of 20. Nearly every type of tissue, including the brain, is susceptible to the inflammatory process that leads through fibrosis to calcification. The exception is the skeleton, which loses its calcium as the soft tissues absorb calcium.

These observations lead to some simplifying ideas about the nature of aging and disease.

Some people who know about the involvement of calcium in aging, stress, and degeneration suggest eating a low calcium diet, but since we all have skeletons, dietary calcium restriction cant protect our cells, and in fact, it usually intensifies the process of calcification of the soft tissues. Statistics from several countries have clearly shown that the mortality rate (especially from arteriosclerotic heart disease, but also from some other diseases, including cancer) is lower than average in regions that have hard water, which often contains a very large amount of either calcium or magnesium.

Many studies have shown that dietary calcium (or vitamin D, which increases calcium absorption) can have very important antiinflammatory effects.

About 25 years ago, David McCarron noticed that the governments data on diet and hypertension showed that the people who ate the most salt had the lowest blood pressure, and those who ate the least salt had the highest pressure. He showed that a calcium deficiency, rather than a sodium excess, was the most likely nutritional explanation for hypertension.

Hans Selye found that some steroids contribute to inflammation and

calcification. Animals could be sensitized to develop calciphylaxis, an intense, localized interaction of inflammation and calcification.

In the 1970s, Constance Martin pointed out that, up to that time, estrogen was known to increase soft tissue calcium, but hadnt been shown to improve bone calcification and strength.

Oxygen deprivation, cyanide poisoning, x-irradiation, and all other sorts of injury also increase the calcium content of soft tissues.

One of Selyes colleagues, G. Jasmin, showed that magnesium deficiency causes inflammation. A deficiency of either calcium or magnesium can stimulate the parathyroid glands to produce more hormone (parathyroid hormone, PTH), which increases calcium absorption, but also removes calcium from the bones. This hormone, responding to a dietary calcium or magnesium deficiency, is an important factor in causing cells to take up too much calcium, and its excess is associated with many inflammatory and degenerative diseases.

Interleukin-6 (IL-6), an inflammatory cytokine which increases with aging, is commonly considered to have an important role in the multiple processes of atrophy in old age. One of the things which can increase the production of IL-6 is the parathyroid hormone (PTH), which increases the amount of calcium circulating in the blood, partly by causing it to be removed from the bones; IL-6 stimulates the process of calcium removal from bones.

Some of the interactions of hormones and other regulatory chemicals are interesting, even though they are normally treated as if they were parts of a machine that operates according to a hidden program written in the genes. Prolactin, which is increased under the influence of estrogen or serotonin, causes the body to lose calcium (drawing it from the bones), and it stimulates the secretion of PTH, which compensates for the calcium loss by increasing its mobilization from bones. Prolactins action on bone is at least partly by increasing IL-6 formation; IL-6 stimulates the release of prolactin. Serotonin and IL-6 stimulate each others secretion, and PTH and serotonin each stimulate the others release..

PTH (like estrogen and serotonin) inhibits cellular respiration and activates glycolysis, lowering the ATP level and shifting the cells metabolism toward the production of lactic acid rather than carbon dioxide. PTH also causes bicarbonate to be lost in the urine.

Since the formation of carbon dioxide lowers the intracellular pH, and the formation of lactic acid raises it (through the reaction of NADH with pyruvate), the proteins in the cell become more strongly negatively charged under the influence of oxygen deprivation, or under the influence of these hormones. In the cell with high pH and increased negative electrical charge, the positively charged calcium ion is absorbed into the cytoplasm. The calcium can enter from the relatively concentrated external fluid, but it can also be released from acidic intracellular stores, the way serotonin is released by a disturbance of pH.

There are several other pro-inflammatory substances, such as the cytokines, that have a similar effect on cellular energy systems.

The antimetabolic actions of PTH mimic those seen in aging and diabetes, and surgical removal of the parathyroid glands has been known to eliminate diabetes. PTH can cause diuresis, leading to loss of blood volume and dehydration, hypertension, paralysis, increased rate of cell division, and growth of cartilage, bone, and other tissues.

Simply eating an adequate amount of calcium and magnesium can alleviate many problems related to stress and aging that are considered serious, such as heart arrhythmia, pancreatitis, and tissue calcification. The antiinflammatory, anti-allergy actions of calcium and magnesium are well established, and there is clear evidence that obesity and various emotional disturbances can result from their deficiency. Chronically high

PTH can produce anemia, by a variety of mechanisms.

Since a very low sodium diet increases the loss of magnesium, by increasing aldosterone synthesis, simply increasing the amount of sodium in the diet can help some people to balance their minerals and minimize stress. During fasting and other intense stress, the kidneys destroy a large amount of protein to form ammonia to maintain their ability to excrete acids, so using a large amount of the alkaline minerals can reduce the protein catabolism.

A diet of milk and fruit, or milk and meat, provides a nutritional balance with generous amounts of calcium and magnesium. Leafy vegetables are a very rich source of magnesium, but they are also a potential source of large amounts of lead and other toxins. In 1960, many people, including the U.S.government, were advocating the use of a largely vegetarian diet for children, because of the amount of radioactive strontium in milk. I compared the amount of strontium in a diet of vegetables that would provide the necessary quantity of calcium and protein, and it was clear that vegetables were the worst source of radioactive strontium, because their ratio of strontium to calcium was much higher than the ratio in milk. The cows were concentrating calcium and protein from the contaminated plant foods, eliminating much of the strontium. This principle still applies to the toxins that are currently found in the U.S. food supply.

Milk has many protective effects besides providing calcium.

Many babies are being given milk substitutes (health food drinks) made from soy or rice, with terrible consequences. The same products used by adults have less disastrous effects in the short term, but are still likely to contribute to degeneration and dementia.

Much of the intracellular magnesium is complexed with ATP, and helps to stabilize that molecule. If cellular energy production is low, as in hypothyroidism, cells tend to lose their magnesium very easily, shifting the balance toward the lower energy molecule, ADP, with the release of phosphate. ADP complexes with calcium, rather than magnesium, increasing the cells calcium content.

Increased intracellular calcium, in association with excess nitric oxide and excitatory amino acids, is involved in several neurodegenerative diseases, including ALS, Alzheimers disease, Parkinsons disease, Huntingtons chorea, and epilepsy. Magnesium, nicotine, progesterone, and many other substances are known to protect against excitotoxic calcium overload, but there is no coherent effort in the health professions to make rational use of the available knowledge.

Respiration and carbon dioxide are the basic antagonists of the PTH. At birth, a baby has practically no PTH, probably because of the high intrauterine concentration of carbon dioxide, but within a few days the PTH rises.

Increased carbon dioxide favors bone formation, and decreased bicarbonate favors the loss of calcium from bone (Canzanello, et al., 1995; Bushinsky, et al, 2001). The use of sodium bicarbonate can stimulate bone formation.

A low protein diet, similar to that eaten by a large proportion of women (0.8 g/kg of body weight) increases PTH, and so probably contributes to the development of osteoporosis and the diseases of calcification. In an extreme protein deficiency, there is a shift towards inflammation, serotonin excess, and excessive clotting, which might be related to the effect of the milder, more common protein deficiency. Many people advocate a low protein diet, specifically to prevent or treat osteoporosis, but the cultures that traditionally have had extremely high protein diets, such as the Masai, are very healthy. Recent studies (see Bell and Whiting, 2002) are emphasizing the importance of animal protein in preventing osteoporosis.

Traditional meat-eating cultures efficiently use the whole animal, including blood, skin, bones, and the various organs, rather than just the muscles. That diet is favorable for calcium regulation, because it provides more vitamin A, D, E, and K, calcium, and gelatin, and less of the pro-inflammatory amino acids, tryptophan and cysteine.

Most loss of calcium from bones occurs during the night. PTH tends to cycle with prolactin, which increases during the night, along with cortisol and the other stress hormones. These nocturnal hormones probably account for the morning stiffness seen in many rheumatic conditions, connective tissue diseases, and in aging.

Progesterone, which increases the carbon dioxide content of the tissues, is remarkably able to inhibit the actions of most of the inflammatory and catabolic mediators, and to protect against degenerative calcification and osteoporosis. It also protects against abnormal clotting. PTH increases platelet calcium concentration, and under some conditions can produce inappropriate coagulation.

Aspirin inhibits the actions of PTH, helping to prevent the calcification of inflamed tissues, and it inhibits the loss of calcium from bones. Aspirin decreases the release of IL-6.

A protein called the PTH-related protein (PTHrP) has the same functions as PTH, but can be produced in any tissue. It is responsible for the hypercalcemia of cancer, and is apparently involved in the frequent metastasis of breast cancer to the bones.

With only a small change in the theory of the nature of a living organism, recognizing the importance of the interactions of metabolites and structural substances, controlled by energetic metabolism, real progress could be made in understanding disease and health. The most important calcium paradox is that medical journals (e.g., *International J. of Cardiology,* Dec., 2002) are still promoting the idea that eating too much calcium causes hardening of the arteries and other diseases of calcification.

REFERENCES

J Am Soc Nephrol 1994 Apr;4(10):1814-9. A role of parathyroid hormone for the activation of cardiac fibroblasts in Uremia. Amann K, Ritz E, Wiest G, Klaus G, Mall G. Thus, PTX abolished and PTH restored intermyocardiocytic changes of experimental uremia. These observations argue for a permissive role of PTH for fibroblast activation and the genesis of the cardiac fibrosis of uremia.

Clin Endocrinol (Oxf) 1976 May;5(3):291-3. Recurrent hormone dependent chorea: effects of oestrogens and progestogens. Barber PV, Arnold AG, Evans G.

Biochem Biophys Res Commun 2001 Feb 23;281(2):277-81. **17 beta-estradiol increases Ca(2+) influx and down regulates interleukin-2 receptor in mouse thymocytes.** Azenabor AA, Hoffman-Goetz L.

Nutr Rev 2002 Oct;60(10 Pt 1):337-41. Elderly women need dietary protein to maintain bone mass. Bell J, Whiting SJ. Researchers who conducted a recent prospective study of older adults reported that animal protein had a protective role for bone, especially in elderly women, whereas plant protein was negatively associated with bone mineral density. Other studies confirm the beneficial effect of increasing dietary protein intake in older women to reduce bone mineral density loss and risk of fracture, suggesting that emphasis should be placed on promoting adequate protein intake in elderly women.

Am J Physiol Renal Physiol 2001 Dec;281(6):F1058-66. Metabolic, but not respiratory, acidosis increases bone PGE(2) levels and calcium release. Bushinsky DA, Parker WR, Alexander KM, Krieger NS. A decrease in blood pH may be due to either a reduction in bicarbonate concentration ([HCO(3)(-)]; metabolic acidosis) or to an increase in PCO(2) (respiratory acidosis). In mammals, metabolic, but not respiratory, acidosis increases urine calcium excretion without altering intestinal calcium absorption, indicating that the additional urinary calcium is derived from bone. In cultured bone, chronic metabolic, but not respiratory, acidosis increases net calcium efflux (J(Ca)), decreases osteoblastic collagen synthesis, and increases osteoclastic bone resorption. Metabolic acidosis increases bone PGE(2) production, which is correlated with J(Ca), and inhibition of PGE(2)

production inhibits this acid-induced J(Ca). Thus metabolic, but not respiratory, acidosis induces the release of bone PGE(2), which mediates J(Ca) from bone.

J Clin Endocrinol Metab 1991 Jan;72(1):69-76. Circadian variation in ionized calcium and intact parathyroid hormone: evidence for sex differences in calcium homeostasis. Calvo MS, Eastell R, Offord KP, Bergstralh EJ, Burritt MF. Serum intact PTH levels showed a significant circadian pattern in both sexes (P less than or equal to 0.001).

J Lab Clin Med 1995 Jul;126(1):81-7. Effect of chronic respiratory acidosis on calcium metabolism in the rat. Canzanello VJ, Kraut JA, Holick MF, Johns C, Liu CC, Madias NE. Chronic metabolic acidosis typically results in hypercalciuria and negative calcium balance. The impact of chronic respiratory acidosis on calcium metabolism has been less well studied. To address this issue, metabolic balance and static bone histomorphometric data were obtained during a 14-day exposure of rats to 10% CO2 (blood pH 7.33, PaCO2 83 mm Hg) and were compared with pair-fed controls. All rats were fed a 0.8% calcium diet. Urinary calcium excretion (mg/period, mean +/- SEM) was increased during both week 1 and week 2 (16 +/- 3 vs 9 +/- 1 and 16 +/- 2 vs 9 +/- 1, CO2 group vs controls, respectively [p < 0.05]). Net intestinal calcium absorption (intake minus fecal excretion) was increased throughout the period of hypercapnia (week 1, 213 +/- 19 mg vs 135 +/- 15 mg; week 2, 135 +/- 16 mg vs 43 +/- 14 mg; and cumulatively, 344 +/- 27 mg vs 178 +/- 20 mg, CO2 group vs controls [p < 0.01]). As a consequence of the marked increment in intestinal calcium absorption during hypercapnia, mean net calcium balance was more positive than that of controls throughout the study (week 1, 197 +/- 18 mg vs 126 +/- 15 mg; week 2, 120 +/- 15 mg vs 34 +/- 15 mg; and cumulatively, 317 +/- 25 mg vs 159 +/- 20 mg, CO2 group vs controls, respectively [p < 0.01]). There were no significant differences in calcium intake, plasma total calcium, immunoreactive parathyroid hormone, 25-hydroxyvitamin D, or creatinine clearance between the two groups.

Mov Disord 1991;6(4):355-7. An unusual cause of recurrent chorea. Caviness JN, Muenter MD. Lee Silverman

Bone 2000 Jan;26(1):79-85. **Correlation of estradiol, parathyroid hormone, interleukin-6, and soluble interleukin-6 receptor during the normal menstrual cycle.** Chiu KM, Arnaud CD, Ju J, Mayes D, Bacchetti P, Weitz S, Keller ET. **Furthermore, IL-6 correlated positively with serum Ca over the entire cycle (p = 0.0091. Serum Ca correlated positively with serum (p = 0.040) and urine (p = 0.006) Dpd. PTH was significantly higher during the FP than in the LP** (p = 0.004). **These data demonstrate that IL-6 and PTH fluctuate with E2, and serum II-6 is associated with PTH levels during the menstrual cycle.**

J Cell Sci 2002 Feb 1;115(Pt 3):599-607. pH-dependent regulation of lysosomal calcium in macrophages. Christensen KA, Myers JT, Swanson JA. Average free calcium concentration in macrophage lysosomes was 4-6x10(-4) M, less than half of the extracellular calcium concentration, but much higher than cytosolic calcium levels. pH-dependent reductions of lysosomal calcium concentrations appeared to result from calcium movement out of lysosomes into cytoplasm, since increases in cytosolic calcium levels could be detected upon lysosome alkalinization.

Adv Neurol 1979;26:123-33. Ovarian steroid hormones and cerebral function. Cogen PH, Zimmerman EA.

J Bone Miner Res 1996 Oct;11(10):1419-29. Stimulation of neonatal mouse calvarial bone resorption by the glucocorticoids hydrocortisone and dexamethasone. Conaway HH, Grigorie D, Lerner UH. In vitro stimulation of bone resorption was observed with the glucocorticoids hydrocortisone and dexamethasone. The 45Ca release stimulated by 1 microM hydrocortisone and 0.1 microM dexamethasone was also inhibited by 10 microM progesterone in a competitive manner and by 1 microM of the antiglucocorticoid RU38486, both of which are modulators of glucocorticoid binding.

J Physiol 2002 Mar 15;539(Pt 3):791-803. MgATP counteracts intracellular proton inhibition of the sodium-calcium exchanger in dialysed squid axons. DiPolo R, Beauge L. The increase in Ca(2+)(i) affinity induced by ATP at acid pH (6.9) can be mimicked by a rise in pH(i) from 6.9 to 7.3 in the absence of the nucleotide.

J Maine Med Assoc 1977 Oct;68(10):370-1 Quadriparesis as an unusual manifestation of hypercalcemia. Dyro FM.

J Clin Endocrinol Metab 1992 Mar;74(3):487-94. Abnormalities in circadian patterns of bone resorption and renal calcium conservation in type I osteoporosis. Eastell R, Calvo MS, Burritt MF, Offord KP, Russell RG, Riggs BL. The serum osteocalcin concentration, a sensitive index of bone formation, increased by about 5% at night in both groups. Urinary deoxypyridinoline excretion, a sensitive index of bone resorption, increased by 48% at night (P less than 0.01) in the normal women, whereas in the osteoporotic women it was 62% higher overall (P less than 0.05), and the increase persisted into the morning. The serum ionized calcium concentration

did not change at night in either group. There was a trend (P = 0.07) for blunting of the nocturnal increase in the serum intact PTH level in osteoporotic women. Thus, the nocturnal serum ionized calcium level is maintained by decreased urinary calcium excretion and increased bone resorption in postmenopausal normal women, but almost entirely by increased resorption in postmenopausal osteoporotic women.

Hypertension 1986 Jun;8(6):497-505. Effects of calcium infusion on blood pressure in hypertensive and normotensive humans. Ellison DH, Shneidman R, Morris C, McCarron DA. Together, these data provide evidence for interactions between dietary sodium intake and the cardiovascular response to calcium. They confirm that hypertensive subjects exhibit enhanced parathyroid gland function even when dietary factors are controlled, and they suggest that these subjects are more sensitive to the cardiovascular effects of short-term calcium infusion.

Yale J Biol Med 1996 Sep-Dec;68(5-6):215-7. Diplopia associated with hyperparathyroidism: report of a case. Forman BH, Ciardiello K, Landau SJ, Freedman JK. A patient with hypercalcemia due to primary hyperparathyroidism presented with diplopia that resolved with surgical removal of his parathyroid adenoma and normalization of his serum calcium values. No previous report of this feature of hyperparathyroidism has been reported.

J Nutr Sci Vitaminol (Tokyo) 1985 Dec;31 Suppl:S15-9. **Aging and calcium as an environmental factor.** Fujita T Calcium deficiency is a constant menace to land-abiding animals, including mammals. Humans enjoying exceptional longevity on earth are especially susceptible to calcium deficiency in old age. Low calcium and vitamin D intake, short solar exposure, decreased intestinal absorption, and falling renal function with insufficient 1,25(OH)2 vitamin D biosynthesis all contribute to calcium deficiency, secondary hyperparathyroidism, bone loss and possibly calcium shift from the bone to soft tissue, and from the extracellular to the intracellular compartment, blunting the sharp concentration gap between these compartments. The consequences of calcium deficiency might thus include not only osteoporosis, but also arteriosclerosis and hypertension due to the increase of calcium in the vascular wall, **amyotrophic lateral sclerosis and senile dementia due to calcium deposition** in the central nervous system, **and a decrease in cellular function, because of blunting of the difference in extracellular-intracellular calcium, leading to diabetes mellitus, immune deficiency and others (Fig. 6)**

Ann N Y Acad Sci 1990;587:371-5. Cytokines and osteoporosis. Fujita T, Matsui T, Nakao Y, Shiozawa S, Imai Y. Conditions associated with immune dysfunction such as aging, corticosteroid therapy, and rheumatoid arthritis are associated with osteoporosis, which is also more common in females than in males, like most of the autoimmune-collagen diseases. Peripheral lymphocyte subsets CD4/CD8 were higher in patients with senile osteoporosis than in the age-matched controls, and returned to normal after 1 month of 1 alpha(OH)vitamin D3 treatment. Plasma interferon reflecting macrophage function decreased with advance in age and increased in response to 1 alpha(OH)D3 treatment. As one of the immunoregulators, vitamin D tends to stimulate the macrophage-natural killer system and suppress the lymphocyte system, stimulating TGF beta and TNF alpha activity. Senile osteoporosis of low turnover thus appears to be associated with vitamin D deficiency, low macrophage function, high CD4 lymphocyte proportion, low IL-1 and high IL-2 activity, low IFN alpha and high IFN gamma activity, and low TGF beta and TNF alpha activity.

Contrib Nephrol 1991;90:206-11. **Calcium, parathyroids and aging.** Fujita T Calcium is unique in its distribution in living organisms with an extremely high hard and soft tissue and extra- intracellular concentration gradient. Calcium **deficiency through stimulating parathyroid hormone secretion tends to blunt such a difference by paradoxically increasing the calcium concentration in the soft tissue and intracellular compartment. Since aging is associated with the** progressive aggravation of calcium deficiency, such blunting also progresses with aging. The dysfunction, damage and death of cells occurring in all diseases **is always associated with a blunting of the extra- and intracellular calcium components. Calcium supplement especially with highly biologically available active absorbable calcium, was associated with the suppression of parathyroid** hormone secretion and the normalization of a such blunting **of intercompartmental distribution of calcium examples in hypertension and diabetes mellitus with evident improvement of clinical manifestations and laboratory tests.**

Presse Med 2001 Apr 7;30(13):653-8. [Hypovitaminosis D: a major worldwide public health problem] Gannage-Yared MH, Tohme A, Halaby G. Mild to moderate hypovitaminosis D causes secondary hyperparathyroidism increasing the risk

of fracture, particularly femoral neck fracture. Vitamin D would also have an antiinflammatory and anticancer effect. Hypovitaminosis D is frequently observed in Europe in the elderly, particularly in the institutionalized population, but is also seen in otherwise healthy younger adults. An estimated 40% of the young European population has some degree of hypovitaminosis D. Finally, the beneficial effect of moderate sun exposure on cutaneous vitamin D synthesis (and psychological well-being) must not be overlooked.

Mol Med 1996 Mar;2(2):204-10. **Parathyroid hormone-related protein is induced during lethal endotoxemia and contributes to endotoxin-induced mortality in rodents.** Funk JL, Moser AH, Strewler GJ, Feingold KR, Grunfeld C. Parathyroid hormone-related protein (PTHrP) is a ubiquitous and highly conserved vasoactive peptide whose role and regulation in normal physiology remain an enigma. Recently, we demonstrated that low-dose endotoxin (LPS) induces intrasplenic, but not systemic, levels of PTHrP; and that tumor necrosis factor, a pro-inflammatory cytokine, is the major mediator of this effect. We have therefore hypothesized that, with higher, lethal doses of endotoxin, PTHrP could be induced in multiple tissues to such a degree that it could contribute to the lethality of septic shock. In response to a near-lethal dose of endotoxin, PTHrP mRNA levels increased acutely in every vital organ examined (spleen, lung, heart, kidney, and liver). Circulating levels of PTHrP also increased, peaking 2 hr after administration of high-dose endotoxin. These **results suggest that PTHrP belongs to the cascade of pro-inflammatory cytokines induced during lethal endotoxemia that is responsible for the toxic effects of** LPS.

J Clin Endocrinol Metab 1998 Feb;83(2):326-32. Serum soluble interleukin-6 receptor and biochemical markers of bone metabolism show significant variations during the menstrual cycle. Gorai I, Taguchi Y, Chaki O, Kikuchi R, Nakayama M, Yang BC, Yokota S, Minaguchi H. Serum soluble interleukin-6 receptor (sIL-6R) showed a significant variation; a rise during the early and late follicular periods followed by a fall during the early luteal period (P = 0.0423, P = 0.0334) and an increase during the mid and late luteal periods. The serum PTH level was significantly higher during the follicular than the luteal period (P = 0.0132).

Calcif Tissue Int 1990 May;46(5):294-9. Effective therapy of glucocorticoid-induced osteoporosis with medroxyprogesterone acetate. Grecu EO, Weinshelbaum A, Simmons R. The results lend support to the hypothesis of a progesterone-glucocorticoid competitive antagonism at the bone level, though other possibilities can be entertained, and suggest MPA as an effective therapy for glucocorticoid-induced osteoporosis in men.

Proc Soc Exp Biol Med 1986 Mar;181(3):438-42. **Forskolin-induced bone resorption in neonatal mouse calvaria in vitro.** Gunasekaran S, Hall GE, Kenny AD **Lactic acid release was increased during the 96 hr of incubation in proportion to the calcium release in the media.**

J Endocrinol 2000 Feb;164(2):129-38. **Estrogen mediates the sex difference in post-burn immunosuppression.** Gregory MS, Duffner LA, Faunce DE, Kovacs EJ. Previous studies in our laboratory have demonstrated that cell-mediated immune function was suppressed in female, but not male, mice at 10 days after burn injury and was mediated, **in part, by increased production of interleukin-6 (IL-6).** Increased circulating **concentrations of E(2) corresponded with suppressed delayed-type hypersensitivity (DTH) and splenocyte-proliferative responses, and increased circulating concentrations of IL-6 in female mice after burn. Ovariectomy** restored the suppressed DTH response and decreased IL-6 concentrations, and administration of exogenous E(2) to both ovariectomized females and intact male mice resulted in a suppressed DTH response. In addition, in vitro **treatment with E(2) suppressed splenocyte proliferation in a macrophage-dependent manner and enhanced macrophage production of IL-6.**

Calcif Tissue Int 1990 May;46(5):294-9. Effective therapy of glucocorticoid-induced osteoporosis with medroxyprogesterone acetate. Grecu EO, Weinshelbaum A, Simmons R.

Nephron 1982;30(3):237-9. Elevated thrombocyte calcium content in uremia and its correction by 1 alpha(OH) vitamin D treatment. Gura V, Creter D, Levi J.

Fortschr Med 1985 Mar 28;103(12):328-30. **[Antiallergic effect of oral calcium.** A clinico-experimental study] [Article in German] Haas PJ.

Randomized Controlled Trial

Acta Univ Carol Med Monogr 1972;53:427-32. The possible role of platelets as trigger in intravascular coagulation associated with acute hyperparathyroidism. Hilgard P, Hohage R, Schmitt W, Minne H, Ziegler R.

Sci Total Environ 1986 Oct;54:207-16. Chemical qualities of water that contribute to human health in a positive way. Hopps HC, Feder GL. The chemical substances in water that make positive contributions to human health act mainly in two ways: (i) nutritionally, by supplying essential macro and micro elements that the diet (excluding water) may not provide in adequate amounts (for example, Mg, I and Zn); and (ii) by providing macro and micro elements that inhibit the absorbtion and/or effects of toxic elements such as Hg, Pb and Cd. In this context, the inverse relationship between hard water and cardiovascular disease will be discussed. Specific data relating hardness and Mg and Ca content of potable waters to specific geographic regions of the U.S.A. will be presented. These data show a strong positive correlation between low Mg content and decreased longevity, and between high Ca and Mg content and increased longevity. In the regions considered, increased longevity correlates strongly with decreased cardiovascular mortality, and the decreased longevity with increased cardiovascular mortality.

Calcif Tissue Res 1977 Oct 20;23(3):241-4. **Proliferation of osteoclasts in rat bone following bleeding and femoral fractures.** Johnell O, Hulth A This rise in the osteoclast population might be due to an increased parathyroid activity released by the trauma, but other factors may be involved. Both bleedings and fractures in rats are followed by hypercalcemia.

Brain Behav Immun 2000 Mar;14(1):49-61. **Modulation of IL-6 production during the menstrual cycle in vivo and in vitro.** Konecna L, Yan MS, Miller LE, Scholmerich J, Falk W, Straub RH. Premenopausal female patients with chronic inflammatory diseases demonstrate changes in disease activity during the MC. **DHEA decreased LPS-induced IL-6 secretion at six of seven time points during the MC (DHEA, p = .047). In contrast, beta-estradiol and testosterone increased LPS-induced IL-6 secretion in six of seven time points** during the MC (significant for testosterone, p = .005). The study demonstrates oscillation of serum IL-6 concentration during the MC and the marked MC-dependent modulation of IL-6 secretion by sex hormones.

Kidney Int Suppl 1983 Dec;16:S204-7. **Pathogenesis of the anemia of uremia: role of secondary hyperparathyroidism.** Massry SG PTH may participate in the genesis of the anemia of uremia through at least **three pathways. These include inhibition of erythropoiesis, shortening survival of RBCs and inducing fibrosis of bone marrow cavity.**

Braz J Med Biol Res 2002 Feb;35(2):229-36. Parathyroid hormone secretion in chronic human endogenous hypercortisolism. Lanna CM, Paula FJ, Montenegro RM Jr, Moreira AC, Foss MC. Osteoporosis is a common manifestation of Cushing's syndrome, but the mechanisms responsible for this abnormality have not been defined. Patients with CH showed an increased PTH response to the hypocalcemic stimulus compared to controls.

Am J Clin Nutr 2000 Jul;72(1):168-73. **A threshold for low-protein-diet-induced elevations in parathyroid hormone.** Kerstetter JE, Svastisalee CM, Caseria DM, Mitnick ME, Insogna KL. **Elevations in PTH developed by day 4 of the diets containing 0.7 and 0.8 g protein/kg but not during the diets containing 0.9 or 1.0 g protein/kg.** Our data suggest that in young healthy women consuming a well-balanced diet, the current recommended dietary allowance for protein (0.8 g/kg) results in short-term perturbations in calcium homeostasis.

J Endocrinol 1995 Sep;146(3):421-9. Effect of oral calcium supplementation on intracellular calcium and plasma renin in men. Lijnen P, Petrov V. Oral calcium supplementation in these men was also accompanied by a reduction in the plasma concentration of intact parathyroid hormone and 1,25-dihydroxyvitamin D3, an increase in 24-h urinary calcium excretion but no change in the plasma total Ca2+ concentration, serum ionized Ca2+ level and plasma phosphate or 25-hydroxyvitamin D3.

Clin Sci (Lond) 1996 Sep;91(3):313-8. Effects of mineral composition of drinking water on risk for stone formation and bone metabolism in idiopathic calcium nephrolithiasis. Marangella M, Vitale C, Petrarulo M, Rovera L, Dutto F. The increase in overall calcium intake due to different drinking water induced modest increases in calcium excretion, whereas oxalate excretion tended to decrease. The changes in oxalate excretion during any

one study period compared with another were significantly related to those in calcium intake. Citrate excretion was significantly higher with the high-calcium, alkaline water. 4. Parathyroid hormone, calcitriol and markers of bone resorption increased when patients were changed from the high-calcium, alkaline to the low-calcium drinking water. 5. We suggest that overall calcium intake may be tailored by supplying calcium in drinking water. Adverse effects on bone turnover with low-calcium diets can be prevented by giving high-calcium, alkaline drinking water, and the stone-forming risk can be decreased as effectively as with low-calcium drinking water.

J Endocrinol 1998 Feb;156(2):231-5. Calcium blood level modulates endogenous nitric oxide action: effects of parathroidectomy in patients with hyperparathyroidism. Martina V, Bruno GA, Brancaleoni V, Zumpano E, Tagliabue M, Fornengo R, Gasparri G, Pescarmona GP. In primary hyperparathyroidism (H-PTH) an increase in platelet free calcium levels is present. After surgery, together with the normalization of calcium levels, NO production also returned to normal values.

Hypertension 1980 Mar-Apr;2(2):162-8. Enhanced parathyroid function in essential hypertension: a homeostatic response to a urinary calcium leak. McCarron DA, Pingree PA, Rubin RJ, Gaucher SM, Molitch M, Krutzik S. Recent reports . . . suggest that increased parathyroid gland function may be one of the more common endocrine disturbances associated with hypertension. Compared to a second age- and sex-matched normotensive population, the hypertensives demonstrated a significant (p less than 0.005) relative hypercalciuria. For any level of urinary sodium, hypertensives excreted more calcium. These preliminary data suggest that parathyroid gland function may be enhanced in essential hypertension.

Am J Med 1987 Jan 26;82(1B):27-33. The calcium paradox of essential hypertension. McCarron DA, Morris CD, Bukoski R. Three disparate observations--that calcium mediates vascular smooth muscle contraction, that calcium channel blockers lower blood pressure, and that increased dietary calcium intake can also ameliorate hypertension--constitute somewhat of a paradox. This evidence, and the paradoxical therapeutic efficacy of both calcium channel blockers and supplemental dietary calcium, can be integrated into a single theoretic construct.

Am J Hypertens 1995 Oct;8(10 Pt 1):957-64. Regulation of parathyroid hormone and vitamin D in essential hypertension. Young EW, Morris CD, Holcomb S, McMillan G, McCarron DA. The maximal stimulated PTH level was significantly higher in hypertensive than normotensive subjects in the absence of measured differences in serum ionized calcium concentration, serum 1,25(OH)2-vitamin D concentration, and creatinine clearance.

J Clin Invest 1995 Apr;95(4):1933-40. **The diurnal rhythm of bone resorption in the rat. Effect of feeding habits and pharmacological inhibitors.** Muhlbauer RC, Fleisch H. This paper shows that, in rats, bone mass can be **increased by feeding habits per se. . . . we previously found a peak of bone resorption following food administration. We now demonstrate that dividing the solid and liquid intake into portions blunts this peak ....** Whether bone mass in humans is also under the control of dietary habits is not known. **If so, an increased meal frequency may be used to prevent osteoporosis.**

Nephron 2001 Dec;89(4):384-90. **Prolonged dietary calcium restriction: a diagnostic approach in idiopathic Hypercalciuria.** Muller D, Eggert P.

Scand J Urol Nephrol 1997 Jun;31(3):275-80. Serum magnesium concentration and PTH levels. Is long-term chronic hypermagnesemia a risk factor for adynamic bone disease? Navarro JF, Macia ML, Gallego E, Mendez ML, Chahin J, Garcia-Nieto V, Garcia JJ. Interestingly, patients with low PTH had a significantly higher serum Mg concentration than patients with adequate or high PTH (2.8 +/- 0.2 mg/dl vs 2.3 +/- 0.1 mg/dl and 2.2 +/- 0.1 mg/dl, respectively, $p < 0.01$). Moreover, regression analysis showed a negative linear correlation between serum PTH level and plasma Mg concentration ($r = -0.6059$, $p < 0.001$).

J Appl Physiol 2001 Jun;90(6):2094-100. Effects of hypercapnia and hypocapnia on [Ca2+]i mobilization in human pulmonary artery endothelial cells. Nishio K, Suzuki Y, Takeshita K, Aoki T, Kudo H, Sato N, Naoki K, Miyao N, Ishii M, Yamaguchi K. Hypocapnic alkalosis caused a fivefold increase in [Ca2+]i compared with hypercapnic acidosis. The hypocapnia-evoked increase in [Ca2+]i was decreased from 242 +/- 56 to 50 +/- 32 nmol/l by the removal of extracellular Ca2+. The main mechanism affecting the hypocapnia-dependent [Ca2+]i increase was thought to be the augmented influx of extracellular Ca2+ mediated by extracellular alkalosis. Hypercapnic acidosis caused little change in PGI2 production, but hypocapnic alkalosis increased it markedly.

Clin Nephrol 2002 Mar;57(3):183-91.. Bone involvement in idiopathic hypercalciuria. Misael da Silva AM, dos Reis LM, Pereira RC, Futata E, Branco-Martins CT, Noronha IL, Wajchemberg BL, Jorgetti V. A negative

correlation was observed between IL-6 levels and Z score of the femoral neck. Bone involvement was detected in a young population with nephrolithiasis demonstrating that a strict follow-up is necessary in order to control hypercalciuria.

Am J Physiol Heart Circ Physiol 2002 Jul;283(1):H193-203. CaMKII-dependent reactivation of SR Ca(2+) uptake and contractile recovery during intracellular acidosis. Nomura N, Satoh H, Terada H, Matsunaga M, Watanabe H, Hayashi H. In hearts, intracellular acidosis disturbs contractile performance by decreasing myofibrillar Ca(2+) response, but contraction recovers at prolonged acidosis.

J R Soc Health 1998 Apr;118(2):103-6. Lessons to be learned: a case study approach. Primary hyperparathyroidism simulating an acute severe polyneuritis. Olukoga A. The case is presented of a 65 year old lady with recent onset of neuromuscular manifestations, comprising paraparesis, areflexia and unsteady gait, along with episodes of slurring of speech and diplopia, later confirmed to be due to severe hypercalcaemia--which itself was caused by primary hyperparathyroidism.

Nippon Ronen Igakkai Zasshi 1989 May;26(3):216-22. **[Calcium and magnesium metabolism in the aged]** [Article in Japanese] Ouchi Y, Orimo H Although serum calcium concentration remains constant during ageing, the plasma **concentration of calcium regulating hormones has been known to show dramatic change with ageing. The plasma concentration of parathyroid hormone increases with ageing, whereas plasma concentrations of calcitonin and active vitamin D metabolite decrease with ageing.** On the other hand, the incidence of **soft tissue calcification is known to increase with ageing.**

J Clin Endocrinol Metab 1978 Sep;47(3):626-32. Calcium-regulating hormones during the menstrual cycle. Pitkin RM, Reynolds WA, Williams GA, Hargis GK. In six subjects with cycle lengths of 27-31 days, PTH levels rose progressively through the follicular phase to a peak at or slightly before the LH surge, then fell progressively through the luteal phase; peak PTH levels were 30-35% above early follicular and late luteal values. One subject experienced a prolonged (44 day) ovulatory cycle characterized by three distinct PTH peaks, each of which coincided with elevations in plasma estradiol level.

Muscle Nerve 1982 Jan;5(1):26-32. **Hereditary polymyopathy and cardiomyopathy in the Syrian hamster. II. Development of heart necrotic changes in relation to defective mitochondrial function.** Proschek L, Jasmin G **Since the mitochondrial respiratory pattern and calcium overload parallel the cardiac degeneration, it is inferred that the cell energy depletion is a functional consequence of an abnormal calcium influx.**

Eur J Endocrinol 1998 Oct;139(4):433-7. **Changes in cytochrome oxidase activity in brown adipose tissue during oestrous cycle in the rat.** Puerta M, Rocha M, Gonzalez-Covaleda S, McBennett SM, Andrews JF. **The involvement of oestradiol in such a cycle is suggested by the fact that oestradiol treatment decreased COX activity to values similar to those found in proestrus.**

Am J Hypertens 1999 Dec;12(12 Pt 1-2):1217-24. Modification of intracellular calcium and plasma renin by dietary calcium in men. Petrov V, Lijnen P. Our data show that the increase in PARA [plasma renin activity] observed in men during oral calcium supplementation is accompanied by a reduction in the intracellular free and total Ca2+ concentration in platelets and erythrocytes and by a decrease in the plasma concentration of intact parathormone and 1,25-dihydroxyvitamin D3.

Arthritis Rheum 2001 Oct;44(10):2338-41. **Association of osteoporosis and cardiovascular disease in women with systemic lupus erythematosus.** Ramsey-Goldman R, Manzi S. These results demonstrate an association between decreased BMD and both an increased carotid plaque index and presence of coronary artery calcification in a small cohort of young women with lupus.

Am J Hypertens 1994 Dec;7(12):1052-7. Dietary calcium reduces blood pressure, parathyroid hormone, and platelet cytosolic calcium responses in spontaneously hypertensive rats. Rao RM, Yan Y, Wu Y.

J Clin Endocrinol Metab 2002. May;87(5):2008-12 Potassium citrate prevents increased urine calcium excretion and bone resorption induced by a high sodium chloride diet. Sellmeyer DE, Schloetter M, Sebastian A.

J Allergy Clin Immunol 1990 Dec;86(6 Pt 1):881-5 **1,25-Dihydroxyvitamin D3 potentiates the decreased response of**

lymphocytes from atopic subjects to agents that increase intracellular cyclic adenosine monophosphate. Ravid A, Tamir R, Liberman UA, Rotem C, Pick AI, Novogrodsky A, Koren R.

Eur J Endocrinol 2002 May;146(5):635-42. **Diurnal rhythm of plasma 1,25-dihydroxyvitamin D and vitamin D-binding protein in postmenopausal women: relationship to plasma parathyroid hormone and calcium and phosphate metabolism.** Rejnmark L, Lauridsen AL, Vestergaard P, Heickendorff L, Andreasen F, Mosekilde L. **With the disclosure of a diurnal rhythm of total plasma 1,25(OH)(2)D, all major hormones and minerals related to calcium homeostasis have now been shown to exhibit diurnal variations.**

Magnes Res 1999 Dec;12(4):257-67. Magnesium deficiency-induced osteoporosis in the rat: uncoupling of bone formation and bone resorption. Rude RK, Kirchen ME, Gruber HE, Meyer MH, Luck JS, Crawford DL. Magnesium (Mg) intake has been linked to bone mass and/or rate of bone loss in humans. Experimental Mg deficiency in animal models has resulted in impaired bone growth, osteopenia, and increased skeletal fragility.

Schweiz Med Wochenschr 1994 Jun 25;124(25):1122-8. **[Hypercalcemia]** Schmid C. **Severe hypercalcemia is mainly caused by inappropriately high concentrations of compounds which promote bone resorption, in particular PTH, PTHrP, or 1,25 (OH)2D3. The major consequences are impaired central nervous system and kidney function (polyuria/dehydration);** the latter, in turn, aggravate hypercalcemia via decreased fluid intake, mobility, and renal calcium clearance.

J Neurophysiol 2002 May;87(5):2209-24. Intracellular pH response to anoxia in acutely dissociated adult rat hippocampal CA1 neurons. Sheldon C, Church J. During perfusion with HCO/CO(2)- or HEPES-buffered media (pH 7.35) at 37 degrees C, 5- or 10-min anoxic insults were typified by an intracellular acidification on the induction of anoxia, a subsequent rise in pH(i) in the continued absence of O(2), and a further internal alkalinization on the return to normoxia. Reducing extracellular pH from 7.35 to 6.60, or reducing ambient temperature from 37 degrees C to room temperature, also attenuated the increases in steady-state pH(i) observed during and after anoxia and reduced rates of pH(i) recovery from acid loads imposed in the immediate postanoxic period. The results suggest that a Zn(2+)-sensitive acid efflux mechanism, possibly a H(+)-conductive pathway activated by membrane depolarization, contributes to the internal alkalinization observed during anoxia in adult rat CA1 neurons. The rise in pH(i) after anoxia reflects acid extrusion via the H(+)-conductive pathway and also Na(+)/H(+) exchange, activation of the latter being mediated, at least in part, through a cAMP-dependent signaling pathway.

Am J Physiol Heart Circ Physiol 2002 Dec;283(6):H2518-26. pH-induced changes in calcium: functional consequences and mechanisms of action in guinea pig portal vein. Smith RD, Eisner DA, Wray S. The effects of changing extracellular (pH(o)) and intracellular pH (pH(i)) on force and the mechanisms involved in the guinea pig portal vein were investigated to better understand the control of tone in this vessel. When pH(o) was altered, the effects on force and calcium were the same irrespective of whether force had been produced spontaneously by high-K depolarization or by norepinephrine; alkalinization increased tone, and acidification reduced it. Because pH(o) changes also lead to changes in pH(i), we determined whether the effects on force could be explained by these induced pH(i) changes. It was found, however, that only with spontaneous activity did intracellular alkalinization increase force. In depolarized preparations, force was decreased, and, with norepinephrine, force was initially decreased and then increased. Thus the effects of pH(o) cannot be explained solely by changes in pH(i). The role of the sarcoplasmic reticulum (SR) and surface membrane Ca(2+)-ATPase on the mechanism were investigated and shown not to be involved. Therefore, it is concluded that both pH(o) and pH(i) can have powerful modulatory effects on portal vein tone, that these effects are not identical, and that they are likely to be due to effects of pH on ion channels rather than the SR or plasma membrane Ca(2+)-ATPase.

Biochem Biophys Res Commun 2002 May 10;293(3):974-8. Arachidonic acid increases intracellular calcium in erythrocytes. Soldati L, Lombardi C, Adamo D, Terranegra A, Bianchin C, Bianchi G, Vezzoli G.. Since arachidonic acid and other polyunsaturated fatty acids influence the activities of most ion channels, we studied their effects on the erythrocyte Ca(2+) influx. AA (5-50 microM) and EPA (20-30 microM) stimulated a concentration-dependent increase in [Ca(2+)](i), deriving from extracellular calcium (1 mM), without affecting the intra- and extracellular pH and membrane voltage. We conclude that AA could activate an erythrocyte voltage-independent Ca(2+) transport via an intermediate product of cyclooxygenase pathway...

BMJ 1991 Mar 30;302(6779):762. Hormone replacement therapy induced chorea. Steiger MJ, Quinn NP. University Department of Clinical Neurology, Institute of Neurology, London.

Nippon Naibunpi Gakkai Zasshi 1991 Dec 20;67(12):1319-38. [Cation metabolism and the effects of circulating factors in pregnancy induced hypertension] Takashima M, Morikawa H, Yamasaki M, Mochizuki M. These data suggest that the increase of p-[Ca2+]i and r-[Na+]i in PIH is important in the initiation and maintenance of hypertension by influencing peripheral vascular resistance, and also various factors in the serum of PIH women may contribute to the accumulation of intracellular ionized calcium in patients with PIH.

Hear Res 2001 Apr;154(1-2):81-7. Effects of gentamicin and pH on [Ca2+]i in apical and basal outer hair cells from guinea pigs. Tan CT, Lee SY, Yao CJ, Liu SH, Lin-Shiau SY. By means of fura-2 microspectrofluorimetry, we measured the intracellular calcium concentration ([Ca2+]i) of OHCs bathed in Hanks' balanced salt solution (pH 7.40) during either a resting state or high K+-induced depolarization. While gentamicin and extracellular acidification (pH 7.14) can separately attenuate this increase in [Ca2+]i in both types of OHCs, their suppressive effects are additive in basal OHCs, but not in apical OHCs.

Biochem Pharmacol 1983 Jan 15;32(2):355-60. Induction of mast cell secretion by parathormone. Tsakalos ND, Theoharides TC, Kops SK, Askenase PW. The biologically active fragment of human parathormone (PTH) and intact bovine PTH were found to induce secretion of both serotonin and histamine from rat peritoneal mast cells in vitro. Intradermal injection of PTH induced immediate increases in vascular permeability suggesting that PTH could induce mast cell secretion in vivo. These results demonstrate that elevated levels of PTH can induce mast cell secretion in vitro and in vivo and suggest a possible role for mast cells in the pathophysiology of non-allergic disease states.

J Neurol Sci 1989 Feb;89(2-3):189-97. Hyperestrogenemia in neuromuscular diseases. Usuki F, Nakazato O, Osame M, Igata A. The cases, comprising bulbospinal muscular disease of the Kennedy-Alter-Sung type, Kugelberg-Welander disease, amyotrophic lateral sclerosis, and Duchenne muscular dystrophy, were all euthyroid males. The baseline levels of serum estrone were significantly higher in all of the patients than in age-matched normal subjects. Serum baseline testosterone, LH and FSH levels were all essentially normal, except low FSH levels in Duchenne muscular dystrophy.

MMW Munch Med Wochenschr 1976 Oct 22;118(43):1395-8. **[Oral application of calcium and vitamin D2 in allergic bronchial asthma**] Utz G, Hauck AM. Within 60 minutes after application, a statistically significant reduction of airway resistance (Rt) and intrathoracic gas volume (IGV), as well as an increase of forced exspiratory one second volume (FEV1) and forced inspiratory one second volume (FIV1) was observed, in comparison with placebo. **It is concluded that calcium, given orally in combination with calciferol, causes a decrease of airway obstruction in patients with allergic bronchial asthma.**

J Urol 1994 Oct;152(4):1226-8. **Urinary incontinence due to idiopathic hypercalciuria in children.** Vachvanichsanong P, Malagon M, Moore ES. In addition to being the most common cause of microhematuria in children, our study demonstrates that idiopathic **hypercalciuria is also frequently associated with urinary incontinence of all types.**

Magnes Trace Elem 1991-92;10(2-4):281-6. **Relation of magnesium to osteoporosis and calcium urolithiasis.** Wallach S Magnesium influences mineral metabolism in hard and soft tissues indirectly through hormonal and other modulating factors, and by direct effects on the processes of bone formation and resorption and of crystallization (mineralization). Its causative and therapeutic relationships to calcium urolithiasis (CaUr) are controversial despite an association between low urinary Mg and CaUr. Recent studies have also found a tendency to low serum and/or lymphocyte Mg levels in CaUr. Despite earlier studies demonstrating an inhibitory effect of Mg supplementation on experimental CaUr in animals and in spontaneous CaUr in humans, at least two properly controlled clinical trials of Mg supplementation have failed to demonstrate a beneficial effect on CaUr frequency. With regard to the skeleton, experimental studies have shown that Mg depletion causes a decrease in both osteoblast and osteoclast activity with the development of a form of 'aplastic bone disease'. At the same time, bone salt crystallization is enhanced by Mg deficiency. Conversely, Mg excess impairs mineralization with the development of an osteomalacia-like picture, and may also stimulate bone resorption independently of parathyroid hormone. Whether or not Mg depletion may be a causal factor in human osteoporosis is also controversial, and there are conflicting reports as to the Mg content of osteoporotic bone. Small decreases in serum and/or erythrocyte Mg in osteoporotic patients have

been reported, and one author has noted improved bone mineral density with a multinutrient supplement rich in Mg. The extant data are sparse and indicate a clear need for more rigorous study.

Semin Dial 2002 May-Jun;15(3):172-86 Calciphylaxis: emerging concepts in prevention, diagnosis, and treatment. Wilmer WA, Magro CM. Several recent reports demonstrate that prolonged hyperphosphatemia and/or elevated calcium x phosphorus products are associated with the syndrome. Protein malnutrition increases the likelihood of calciphylaxis, as does warfarin use and hypercoagulable states, such as protein C and/or protein S deficiency.

J Clin Lab Anal 1998;12(3):145-9. A proposal for standardizing urine collections for bone resorption markers measurement. Zaninotto M, Bernardi D, Ujka F, Bonato P, Plebani M. The findings suggest that nocturnal collection and first morning void samples provide the most reliable data on the rate of bone degradation, possibly showing bone loss not only in osteopenic patients but also in women with a low T-score.

Am J Physiol Renal Physiol 2001 Aug;281(2):F366-73. Increased CO(2) stimulates K/Rb reabsorption mediated by H-K-ATPase in CCD of potassium-restricted rabbit. Zhou X, Nakamura S, Xia SL, Wingo CS.

Sci Total Environ 1981 Apr;18:35-45 Water hardness and mortality in the Netherlands. Zielhuis RL, Haring BJ. The hypothesis that the Ca and Mg deficiency in areas with soft drinking water increases the risk of I.H.D. death rate was supported by the finding that food loses more Ca and Mg when it is cooked in soft water as compared to cooking in hard water. However, investigation of a group of 17 municipalities of which mortality and water quality data are known for three periods, 1958-1962, 1965-1970 and 1971-1977, showed that the inverse statistical relation between I.H.D. Mortality and water hardness still existed but with decreasing significance of correlation coefficients.

J Clin Endocrinol Metab 1980 Dec;51(6):1274-8. Serotonin stimulates adenosine 3',5'-monophosphate accumulation in parathyroid adenoma. Zimmerman D, Abboud HE, George LE, Edis AJ, Dousa TP. Since cAMP acts as a mediator of parathyroid hormone (PTH) release, our results suggest that serotonin could be one of the factors regulating PTH secretion and/or contributing to PTH hypersecretion in various forms of primary hyperparathyroidism.

Cas Lek Cesk 1997 Jul 30;136(15):459-63. **[New drugs with positive effects on bones]** [Article in Czech] Zofkova I, Kanceva RL. Magnesium influences bone in different ways. **It activates osteoblasts, increases bone mineralization, and enhances the sensitivity of target tissues (incl. bone) to PTH and 1,25(OH)2 vitamin D3,** Under certain conditions however, magnesium can stimulate bone resorption. A more potent factor than magnesium is stroncium, which not only activates osteoblats but decreases the number of osteoclasts, thus abolishing bone resorption and enhancing formation. **Bicarbonates are also favourable for bone. NaHCO3 together with potassium citrate stimulates osteoblasts and enhances bone mineralisation.**

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