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CALCIUM AND MAGNESIUM DEPOSITS IN DISEASE

by

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I. INTRODUCTION

Abnormal mineral deposits in disease are mostly calcareous, occurring in areas of tissue damage that can be caused by magnesium (Mg) deficiency, or by hormones, stress or drugs that cause Mg loss, or by other injurious factors. Degrees of calcinosis depend on calcemic and/or phosphatemic elements in the diet, and the extent of injury. Perivascular Mg-deficiency induced lesions that develop in genetic cardiomyopathies (CMP) are subject to calcification. In arteriosclerosis, calcium (Ca) is the major mineral deposit but Mg has also been found. Urinary calculi may be renal tubular calcific microliths, and larger stones in renal pelvis, ureters and bladder. Urolithiasis of urinary tract infections are Mg-ammonium-phosphate. Abnormal calcifications can occur with or without hypercalcemia and Mg deficiency. Chondrocalcinosis, or other articular ectopic calcification, sometimes occurs in patients with genetic renal Mg-wasting and hypomagnesemia. Normal serum Ca and Mg is usual with other calcinoses - of skin, subcutaneous tissue and other soft tissues, including myositis ossificans progressiva or traumatica, in which true bone forms in calcinotic ligaments, tendons and skeletal muscle. Hypercalcemia of renal failure is apt to be complicated by metastatic calcinosis.

II. MINERALIZATION OF ARTERIES AND HEART: EXPERIMENTAL ARTERIOSCLEROSIS

A. Atherogenic and/or calcemic diets

Most dietary cardiovascular (CV) disease models have utilized atherogenic diets that affect medium to large arteries. Fat-rich diets, with added vitamin D and/or that modified Ca, Mg, and/or phosphorus (P) intakes produced intimal, subintimal, and medial lesions including fragmented elastica and fibroblastic thickening; Ca loading caused calcification of the damaged elastica, that was prevented by added Mg (Vitale et al., 1957; 1959; 1961; 1963; Nakamura et al., 1960; 1965). Fat, vitamin D and Ca increase Mg requirements, thereby increasing the risk of Mg deficiency (Seelig, 1981; 1986). Vitamin D2 excess was found early to cause generalized arterial calcification, focal myocardial necrosis and Ca deposition (Selye, 1929). Studies with swine fed increasing amounts of vitamin D3 have shown that at the high doses that cause calcific arterial lesions, Mg supplementation was protective (Ito et al., 1986; 1987).

Interrelationships of Mg with fat metabolism are applicable to the atherogenic process (Rayssiguier, 1981; 1984; 1986; Rayssiguier et al., 1989; see also Chapter 3-E of this Part Four). The earliest lesion in the arterial wall, that is caused by Mg deficiency, is of the elastin, the site of initial calcification. Suppression of development of atherosclerosis in cholesterol-fed rabbits by high dietary Mg has also been attributed to the Ca-blocking effect of Mg (Orimo and Ouchi, 1990).

B. Cardiovasopathic diet and spontaneous myocardial infarction
A diet that was low in Mg, potassium (K^+) and chloride (Cl^-), and high in sodium (Na^+), phosphate (PO_4), fat, protein, and vitamin D, caused hyperlipemia, atherosclerosis, hypertension, and myocardial infarction (MI) in 80-90% of cocks, rats and dogs (Sos et al., 1960; 1964; Rigo et al., 1961; 1963; 1965). Despite normal Ca intake and serum Ca, these animals had 12% increased myocardial Ca; their myocardial Mg fell 19%. Reducing only fat intake lowered the MI incidence to 60%; removing only vitamin D reduced the MI incidence to 40%; normalizing salts reduced its occurrence to 13%.

C. Phosphate-loading diets
High PO_4 intake intensifies Mg deficiency (review: O'Dell, 1960). In combination with dihydrotachysterol, PO_4 salts, especially in Mg-deficient animals, induced calcification of aorta and coronaries, and of perivascular myocardium, lesions that were also protected against by Mg and K (Selye, 1958a; 1958b; Bajusz and Selye, 1959; Mishra, 1960). The $NaPO_4$-mineralocorticoid-cardiac necrosis model, like cardiac glycoside-, vitamin D- and catecholamine-excess models of cardiac necrosis and calcinosis, were also protected against by Mg and K (Selye, 1958a; 1961; 1969).

Parathyroid hormone (PTH) with a $NaPO_4$ salt (Selye, 1958c; Lehr, 1963), or stimulation of PTH or adrenal medullary or cortical secretion, as occurs in renal damage or nephrectomy (Lehr, 1959) causes subintimal arterial damage with calcification of the elastica.

D. Experimental magnesium deficient diets
Adverse effects of Mg deficiency alone on the CV system are difficult to define, because control rations fed to rats are often high in Ca (sometimes with a Ca/Mg ratio of 500/1), PO_4 and vitamin D (Larvor, 1971). Mg-deficient rats commonly develop hypercalcemia, unlike the more common hypocalcemia of most other animals and humans. Vascular lesions of Mg-deficient animals, not otherwise challenged, are mainly of small arteries and arterioles, usually identified in the heart (Table 1). Arteriolar lesions are predominantly of the elastica, the first site of Ca deposition, and of other intimal and subintimal tissues (Lowenhaupt et al., 1950; Mishra, 1960; Seta et al., 1965; Hungerford and Bernick, 1980; reviews: Seelig and Haddy, 1980; Seelig, 1980). In Mg-deficient dogs, intimal and medial lesions were also seen, as well as increased Ca deposition, despite hypocalcemia (Bunce et al., 1962; Featherston et al., 1963; Morris et al., 1963; Wener et al., 1964). Arterial calcification was increased when Mg-deficient dogs also received vitamin D or intravenous Ca loads (Syllm-Rapoport and Strassberger, 1958; Unglaub et al., 1959). Elastica degeneration and widespread calcification developed when the usual diets provided vitamin D excess (Gillman and Gilbert, 1956; review: Seelig, 1969).

E. Perivascular myocardial lesions of magnesium deficiency
Mg-deficient hypercalcemic rats or hypocalcemic dogs had myocardial lesions around affected small coronaries (Table 2). Electron microscopic (EM) examination of the perivascular lesions disclosed the earliest damage to be mitochondrial and sarcosomal swelling and distortion (Mishra, 1960; Mishra and Herman, 1969; Heggtveit et al., 1964; Heggtveit, 1965a). Abnormal sarcosomes of Mg-deficient ducks contained more Mg than did normal sarcosomes from controls, possibly indicating unavailability of that Mg for coupling of oxidation to phosphorylation (DiGiorgio et al., 1962). Ca accumulation, as granular electron-dense particles, began before cell death (Heggtveit et al., 1964). A study with isolated rabbit myocardial mitochondria suspended in media containing different amounts of Ca and Mg indicated that Mg modulates mitochondrial Ca uptake and prevents

Table 1

Coronary Arteriolar Damage of Magnesium Deficiency and Perivascular Myocardial
Lesions not Complicated by Calcemic or Atherogenic Diet

Arteriolar intima, subintima, media
    Endothelium: edema, hypertrophy, hyperplasia
    Interstitium: edema, cell-infiltration
    Elastica: thinned, fragmented, disrupted, fat globules, +/- calcification
    Media: edema, necrosis, disrupted, hyperplastic

Endocardium and myocardium
    Endocardium and valves: fibrosis; malformations
    Myocardium: mitochondrial swelling, distortion; electron-dense particles: Ca; Mg?
    edema, cell-infiltration, focal necrosis, collagen deposition, +/- calcification

Derived from studies with *cows* and *ewes*: Arnold and Fincham (1950), Lynd et al. (1965), Willers et
al. (1965), Herd (1966); *rats*: Heggtveit et al. (1964), Heggtveit (1965); *hamsters*: Bloom and
Ahmad (1988), Bloom (1989); *dogs*: Syllm-Rapoport and Strassberger (1958), Unglaub et al. (1959),
Bunce et al. (1962), Featherston et al. (1963), Morris et al. (1964); *rabbits*: Orimo and Ouchi (1990);
swine: Ito et al. (1986; 1987).

Table 2

Arteriolar and Perivascular Myocardial Damage of Magnesium Deficiency
(usually with intensification by high Ca and /or vitamin D diet; protection by high
magnesium intakes)

Endocardium and intimal endothelium
    Edema, hypertrophy, hyperplasia

Interstitium
    Edema, cell-infiltration, collagen increase

Elastica
    Thinned, fragmented, disrupted, lipid droplets, calcification

Smooth muscle
    Disrupted, degenerated, hyperplastic

Myocardium
    Earliest: perivascular mitochondrial damage and calcification
    Then: cell-infiltration, focal necrosis, fibrosis, calcification, Purkinje fiber
    degeneration and calcification

Derived from studies with *calves and cows*: Moore et al. (1938), Blaxter et al. (1954), Larvor et al.
(1964); *rats* (all included because base diets high in Ca): Lowenhaupt et al. (1950), Vitale et al.
(1957; 1959; 1961), Mishra (1960a, 1960b), Sos et al. (1960), Rigo et al. (1961; 1963), Ko et al.
(1962), Heggtveit et al. (1964), Heggtveit (1965a; 1965b), Sos (1965), Nakamura et al. (1960;
1965), Seta et al. (1965), Britton and Stokstad (1970), Hungerford and Bernick (1980), Mishra and
Herman (1960), Rayssiguier (1984); *dogs*: Syllm-Rapoport and Strassberger (1958), Unglaub et al.
(1959), Bunce et al. (1962) Featherston et al. (1963), Morris et al. (1963), Sos et al. (1964), Wener
et al. (1964); *swine*: Ito et al. (1986; 1987).

formation of destructive Ca crystals (Sordahl and Silver, 1975). This is consistent with Mg's protection against the necrotizing effects of Ca- on Mg-deficient myocardial cells (Lehr, 1965; Lehr et al., 1975; Janke et al., 1975).

Mitochondria can sequester large amounts of Ca; interaction of excess Ca with mitochondrial membranes can cause significant uncoupling of oxidative phosphorylation (Schwartz, 1971/1972). Mg has long been known to preserve the mitochondrial structure, preventing Ca-induced mitochondrial swelling (review: Lehninger, 1959). Cardiac mitochondrial membrane lesions favor massive Mg accumulation with inorganic PO_4, which can precipitate (Brierley, 1967).

In Mg-deficient hamsters, the earliest myocardial change was increased Na, that was followed by increased Ca, and then frank calcification (Bloom and Ahmad, 1988; Bloom, 1989). The authors proposed that Mg deficiency inhibited Na,K-adenosine triphosphatase (ATPase) activity, increasing Na-Ca exchange, with resultant high tissue Ca levels, which increased myocardial vulnerability to ischemia and MI. A Ca-channel blocker (nifedipine), supplied to severely Mg-deficient hamsters, ameliorated the myocardial lesions. They were augmented by digoxin, which inhibits Na,K-ATPase activity, raises cardiac Ca, and lowers cardiac Mg (Dunham and Glynn, 1961; Schwartz and Laseter, 1964; review: Seelig, 1972). Mg-deficient mice, given nifedipine, were also protected against Ca deposition in CV tissues (Sakaguchi et al., 1992).

F. Stress and catecholamines

Stress of all types may reduce tissue Mg and raise tissue Ca (reviews: Seelig, 1980; Classen, 1981). Cold stress induced cardiac damage and Ca deposition in Mg-deficient rats (Heggtveit, 1965b). Catecholamines, whether secreted or injected, increase myocardial Ca, a normal stimulant of inotropic activity (Nayler, 1967; Reuter, 1974), and reduce myocardial Mg. They can cause myocardial damage and calcification in Mg-low animals (Bajusz and Selye, 1959; Mishra, 1960; Bajusz, 1965; Lehr, 1965; 1969). Alpha-adrenergic agents (epinephrine or phenylephrine), or the beta-adrenergic agent (isoproterenol), cause myocardial Mg loss, preceding sarcosomal swelling, and severe damage to mitochondrial cristae, and then Ca accumulation (Lehr et al., 1966; 1967; Lehr, 1969). Noise stress, which intensifies the norepinephrine secretion caused by Mg deficiency, has been shown to increase cyclic adenosine monophosphate with resultant increase of permeability of intracellular (ic) membranes that might be accountable for abnormal increase, not only of myocardial Ca, but also of Mg (Günther, 1981).

G. Ischemia and hypoxia

Mitochondrial lesions of ischemic hearts resemble those of Mg deficiency (Heggtveit, 1965b; Heggtveit and Nadkarni, 1971). The earliest EM changes have been correlated with low myocardial Mg and accumulation of Ca (Lehr et al., 1966; Lehr, 1969). Dense granular particles, an important feature of irreversible ischemia-induced myocardial damage, seem to be predominantly $CaPO_4$ precipitates (Shen and Jennings, 1972), but might have Mg in the complexes as well (Jennings, 1969). This premise is supported by the elevation of myocardial Mg after 2½ minutes of cardiac arrest in guinea pigs subjected to anoxia (Hochrein et al., 1967), that can be assumed to be as unavailable PO_4 precipitates (Seelig, 1972).

H. Arterio-cardiomyopathy of genetic disorders in animals
1. Myocardial degeneration

A strain of muscular dystrophic hamsters that develops focal myocardial degeneration before maturity exhibited decreased Mg and elevated Ca in the myocardium before the lesions developed (Bajusz and Lossnitzer, 1968). As myocardial levels of catecholamine rose (Angelakos, 1968; Angelakos et al., 1970/1972), so did the levels of Ca.

2. Diabetes mellitus

Cardiac calcification with low myocardial Mg has been reported in diabetic rats and mice on their stock diets (Hamuro et al., 1970; Nagase et al., 1989; Nakagawa et al., 1989). A diet

low in Mg and high in P rised the myocardial Ca to 400 times normal; added Mg or reduced dietary P prevented the calcification (Hamuro et al., 1970; Hamuro, 1971) and suppressed the heart disease of diabetic mice (Nagase et al., 1989). Mechanisms by which diabetes increases myocardial Ca to pathologic degrees are under study, both with genetic and induced diabetes. Myofibrillar Mg and Ca-stimulated ATPase activities are depressed in diabetic rat hearts (Pierce and Dhalla, 1985). The abnormal Ca accumulation of diabetic rats might reflect insuffient Mg, which functions as a second messenger for insulin that is involved in ion translocation (Lostroh and Krahl, 1974), and/or be caused by defective sarcolemmal Ca pump (Heyliger et al., 1987). Diabetic rats also have decreased myocardial calmodulin activity that may contribute to reduced (Ca + Mg)-ATPase and Ca transport activities (Levine et al., 1990). The greater vulnerability of diabetic rabbits to isoproterenol-induced damage of myocardial mitochondria was attributed to their increased myocardial Ca (Bhimji and McNeill, 1989).

III. MINERALIZATION OF HUMAN ARTERIOSCLEROTIC ARTERIES

A. Arterial and myocardial lesions, and mineral deposition, with aging

Medial elastica degeneration and calcification preceding formation of atheromata was observed to increase with advancing age in human autopsy material: medial calcification was seen in 4% of those 20-30 years of age at death, in 27% of those 30-40 years of age, and in 80% of those in their nineties (Blumenthal et al., 1950). It was pointed out (Lansing et al., 1950; Lansing, 1952) that the cholesterol deposition of atherosclerosis is preceded by changes in arterial elastic tissue. Progressive splitting and fraying of elastic fibers of internal elastica was noted in autopsied subjects at 20 years of age, and increased with aging. The damaged elastica had an affinity for Ca. Damaged calcified elastic tissue was seen in plaque-free coronaries; arterial plaques were not seen without elastica calcification. Deterioration and calcification of medial elastic tissue was seen in all major arteries. The albuminoid fraction of the aorta (collagen, elastin) showed progressive Ca increase with increasing age; atherosclerotic aortas had a two-fold increase in Ca, and decreased Mg in the most highly atherosclerotic arteries (Miller et al., 1953). These lesions resemble those described in a survey of 450 young American men (18 to 39 years of age), who died in the military with coronary arterial disease, 336 of whom had no gross MI. It was considered likely that lipid deposition, in which minerals were often found, was secondary to intimal fragmentation of internal elastic lamellae and fibrosis (Yater et al., 1948).

Lifelong Mg inadequacy might contribute to early and late arterial lesions with arterial calcification (Seelig, 1964; 1972; 1980; 1986; Seelig and Heggtveit, 1974; Seelig and Haddy, 1980). The similarity of hypoxic and ischemic myocardial damage to that of Mg deficiency (vide supra) and the efficacy of Ca-channel blockers in treatment of coronary insufficiency and hypertension suggest that low Mg/Ca ratios might contribute to these clinical disorders. It is also possible that the risk is intensified by vitamin D: high intake or hyperreactivity to vitamin D (DeLangen and Donath, 1956; Linden, 1972; 1974; 1977; Seelig, 1969; 1980).

B. Infantile and juvenile cardiovascular calcification

Intimal, subintimal, and medial fibrous proliferation and elastica degeneration, sometimes calcified (occasionally generalized, but more commonly only of the coronaries) has been reported in about 3,000 infants who were stillborn, or who died suddenly or in the first two and a half years of life (review and tabulations: Seelig, 1980). Although early infantile arterial lesions resemble those of experimental Mg deficiency, that cannot be proved as an etiologic factor since few biochemical data were reported in those cases. Whether Mg insufficiency during pregnancy, or a metabolic defect in Mg absorption (Paunier and Radde, 1965; Friedman et al., 1967; Nordio et al., 1971; Haijamae and MacDowall, 1972; Woodard et al., 1972), possibly genetic (Stromme et al., 1969; Salet et al., 1970; Vainsel et al., 1970), might have been contributory, is speculative. Pediatric coronary and generalized calcific arteriosclerosis also resembles that of hypervitaminosis D; hypercalcemia induction (as from hyperreactivity to vitamin D and/or hyperparathyroidism) might be a predisposing condition (Lightwood, 1932; Brown and Richter, 1941; Andersen and Schlesinger, 1942;

Field, 1946; Stryker, 1947; Mant et al., ~~1952, Wahlgren, 1952, Andersen, 1954, Moran~~ and Becker, 1959; Rashkind et al., 1961; Fraser, 1967; Meyer and Lind, 1972).

C. Cardiovascular calcification of diabetes mellitus
Diabetes mellitus causes Mg loss and lowers serum and cell Mg levels (Flink, 1956; Durlach and Collery, 1984; Petri and Perry, 1986; Gunn and Burns, 1987; Paolisso et al., 1990), that can contribute to diminished elasticity and increased Ca content of arterioles - features of diabetic premature CV disease (Altura et al., 1979), as well as more widespread calcinosis. Studies in animal diabetes are elucidating involved mechanisms (vide supra).

D. Cardiovascular calcification of renal failure
Uremic cardiovascular disease is characterized by medial degeneration and calcification, rather than atheromata. Calcific CMP occurs in advanced renal failure (Terman et al., 1971; Arora et al., 1975; Meema et al., 1987). Rabbits with induced chronic renal failure had increased serum Ca despite decreased intestinal Ca absorption (Tvedegaard, 1987). Their absorption and serum levels of PO_4 were both increased, and morphologic changes of elastica developed early in all major arteries, including coronaries, followed by degeneration and mineralization, with accumulation of Ca, PO_4, and Mg.

IV. CALCIFICATION OF KIDNEYS; UROLITHIASIS

A. Factors influencing urine stone formation
The formation of Ca oxalate uroliths, the most common form of kidney stone in humans, is influenced by several factors, among which is the urinary concentration of Mg. Adding Mg salts to urine has long been known to increase solubility of Ca oxalate (Hammarsten, 1929). This effect, seen at high and at physiologic Mg levels, (Hallson et al., 1982; Li et al., 1985), is enhanced by citrate (Achilles et al., 1988), and is effective at all oxalate concentrations (Kohri et al., 1988). Mg is more effective in preventing formation of the monohydrate form of Ca oxalate crystals than the dihydrate form, in vitro (Oka et al., 1987). Mg-deficient rats given the hyperoxaluric agent, ethylene glycol, developed Ca oxalate-monohydrate crystals, that were adherent to organic material in the tubules (Rushton and Spector, 1982). Urine of normally fed rats given ethylene glycol contained Ca dihydrate oxalate, without intraluminal deposits.

    Organic substances and their interactions influence Ca crystal formation in urine. Pyrophosphate (PP) increases the formation of Ca oxalate (Finlayson, 1974), but paradoxically inhibits crystallization of the amorphous form of $CaPO_4$ hydroxyapatites and of Ca oxalate (Fleisch and Bisaz, 1962; Russell et al., 1964). The nidus for Ca precipitation has been shown to be mucopolysaccharides in Mg-low media (Robertson et al., 1973), as well as in nephrocalcinosis of vitamin D toxicity (Konetzki et al., 1962). A mucoprotein has been identified as the matrix for Ca oxalate renal deposition in Mg deficiency (Seelig and Bunce, 1972; Bunce and King, 1980). Despite the hypercalcemia of excess PTH or vitamin D, stones are relatively uncommon in both, possibly because of increased urine citrate levels in each condition (Kushner, 1956; Lifshitz et al., 1967a).

    Pertinent to prevention by parathyroidectomy of renal calcinosis in rats fed diets low in both Ca and Mg (Heaton, 1964; Heaton and Anderson, 1965) and of that caused by high PO_4 intakes (Meyer and Forbes, 1967), - which causes hyperparathyroidism (Clark and Rivera-Cordero, 1972a; 1972b; Krook et al., 1975) - is the effect of PTH on bone. It mobilizes bone minerals and depolymerizes the glycoprotein ground substance of bone and cartilage (Engel, 1952), making available mucoprotein in which Ca is deposited in the kidneys. Increasing both Ca and PO_4 intakes, keeping the P/Ca ratio at < 1, increased renal calcinosis (Hoek et al., 1988). Lowering the P/Ca ratio further by raising the Ca intake reduced renal Ca deposition but increased body Ca retention.

B. Renal calcinosis and uroliths in experimental mg deficiency
Deposition of Ca microliths in the corticomedullary region of kidneys of Mg-deficient rats has long been known (Cramer, 1932; Brookfield, 1934; Lowenhaupt, 1950; Bunce et al., 1962; 1974; 1980; Giacomelli et al., 1964; Battifora et al., 1966; Goulding and Malthus,

1969; Wang et al., 1969) and attributed to the high Ca/Mg ratio of the diet (Tufts and Greenberg, 1937; MacIntyre and Davidson, 1958). It occurs mostly in the loop and ascending limb of the loop of Henle (Whang et al., 1962; Welt, 1964; Welt and Gitelman, 1965; Oliver et al., 1966; Sarkar, 1988), particularly when the usually high Ca ration was supplemented with milk or other sources of Ca (Featherston et al., 1963) or with nutrients that increased Mg requirements (Hellerstein et al., 1957; Vitale et al., 1959; Lifshitz et al., 1967b). Furosemide, the loop diuretic which inhibits Mg reabsorption, intensified nephrocalcinosis in moderately Mg-deficient rats (Grimm et al., 1990).

Profound Mg deprivation (with a diet providing 0.25 mM Mg and 150 mM of Ca: a 600/1 ratio) caused renal tubular mitochondrial swelling beginning by the third day, cell necrosis by 12-20 days, and ic and luminal Ca deposits (Hess et al., 1959). EM examination of the kidneys of rats fed a diet with a similarly high Ca/Mg ratio showed fewer mitochondria, and tubular calcinosis (Mishra, 1960; Smith et al., 1962). Even with a 10-fold less Ca/Mg disparity, tubules were damaged and Ca was deposited (Kashiwa, 1961). With a base diet providing a 60/1 Ca/Mg ratio, six times as much Mg was needed to limit renal calcinosis in rats (Bunce et al., 1963). The prevention of tubular microliths by high Mg intakes has been affirmed in more recent studies: to ascertain how to limit nephrocalcinosis in rats on purified diets (Harwood, 1982), to quantify the degree of Mg deficiency that causes uroliths in renal tubules (Fischer et al., 1984; Classen and Fischer, 1988), and to determine the Ca/P/Mg ratios that should be provided in stock diets to avoid renal calcinosis in control rats (Ritskes-Hoitinga et al., 1989).

Deposition of Ca-oxalate in the kidneys of Mg-deficient rats was early speculated to be enhanced by deficiency of B vitamins, particularly vitamin B6 (Greenberg, 1939). Pyridoxine deficiency was proved to enhance Ca oxalosis lithiasis in rats and cats decades later (Gershoff et al., 1959; Gershoff and Andrus, 1961; Lyon et al., 1966) and in the last decade (Kridl et al., 1986).

C. Renal calcinosis in diabetic animals

Severe and consistent calcinosis in the corticomedullary region of the kidneys, accompanied by decreased glomerular filtration rate, decreased urea clearance, and hyperphosphatemia are prominent among metastatic calcifications in diabetic mice. These changes were completely prevented by Mg alone (Hamuro et al., 1970; Hamuro, 1971).

V. URINARY TRACT STONES IN HUMANS

A. Epidemiologic observations

The increased prevalence of Ca oxalate uroliths in areas of the developed world where the Mg intake is low (Grossman, 1938; Prien, 1965; 1971; Hradec, 1989; reviews: Seelig, 1980; Kodama and Ohno, 1989) coincides with that of CVD. Low Mg intake (i.e. in soft water areas in the U.S.A. (Landes et al., 1977; Melnick et al., 1971), and use of Mg-poor, PO_4-rich fertilizers in north and central Europe) and administration of vitamin D have been implicated in the rise in calcific urolithiasis since the late 1920s (Linden, 1972; 1977). Struvite stones (Mg ammonium phosphate calculi), that are associated with urinary tract infections, are infrequent in industrialized, but more common in undeveloped lands (Kodama and Ohno, 1989).

B. Clinical urolithiasis and nephrocalcinosis

A low urinary Mg/Ca ratio predisposes to Ca oxalate urolithiasis. Patients with hypercalciuria have been shown to have stones comprised of Ca oxalate mixed with $CaPO_4$; those who excreted normal amounts of Ca had essentially pure Ca oxalate stones (Grases et al., 1990). Both groups had low urinary Mg and citrate concentrations. Fewer than half of Ca stone patients have normal urine Mg levels before treatment; Ca loading of kidneys intensifies the subnormal urinary Mg/Ca ratio (Bataille et al., 1985; Labeeuw et al., 1986). Conditions that cause Mg deficiency are associated with urolith development. For example, they have developed in patients who had intestinal resections or bypass for obesity (Hessov et al., 1981) and in treatment of ulcerative colitis (Stelzner et al., 1990). Impaired tubular reabsorption of Mg has been found in Ca oxalate stone formers (Revusova et al.,

Nephrocalcinosis has been observed in infants and children who are hyperreactive to vitamin D, in adults receiving high-dosage vitamin therapy, and in patients with hypercalcemia from metabolic or endocrinologic disorders (Lightwood, 1935; Danowski et al., 1945; Ferris et al., 1961; Drummond et al., 1964). Infants and children who died during treatment with high dose Ca and/or who had hypervitaminosis D had intraluminal Ca deposition predominantly in regions of the kidneys where most Mg tubular reabsorption occurs (Rhaney and Mitchell, 1956; James, 1956; Kushner, 1956; Shanks and MacDonald, 1959; Taitz et al., 1966; Paunier et al., 1968; Vainsel et al., 1970). Renal Mg wasting has been an accompanying finding in children with hypercalciuria and renal tubular acidosis, with and without nephrocalcinosis (Michelis et al., 1972; Manz et al., 1979; Richard and Freycon, 1992). Familial incidence of renal Mg wasting has been reported (Gitelman et al., 1966; Michelis et al., 1972; Sann et al., 1975; Rodriguez-Soriano et al., 1987).

When very low birth weight infants or those born to diabetic mothers are treated for convulsions with Ca salt infusions, or are fed Ca-enriched milk, as they often are to manage neonatal hypocalcemia and hypoparathyroidism - which may be Mg-deficit induced (Niklasson, 1970; Tsang et al., 1973; David and Anast, 1974; Anast et al., 1976; Mimouni et al., 1986; 1990) - they are at risk of renal calcinosis (Venkataraman et al., 1988). Since hypercalcemic rats and infants have exhibited microliths in the ascending limb of the loop of Henle, the main site of renal reabsorption (Brunette et al., 1974; Quamme et al., 1980; Massry, 1981; Quamme, 1981; 1986), Ca treatment of Mg-deficient infants may predispose to renal Mg wasting.

VI. SOFT TISSUE MINERALIZATION - DISEASES

Clinical syndromes that, despite minimal inflammation and normal serum Ca and phosphate, are characterized by substantial fibrosis and calcinosis in areas of skin, subcutaneous tissues, ligaments, tendons, and skeletal muscle, are metabolic disorders in which hydroxyapatites of $CaPO_4$ and other complexes of Ca are deposited in soft tissues. Except in chondrocalcinosis, which is associated with renal Mg wasting with renal calcinosis, visceral or CV calcinosis does not occur. Serum Ca and phosphate levels are usually normal.

A. Mechanisms

PP - which inhibits transformation of amorphous $CaPO_4$ into the crystalline form that is involved in mineralization of cartilage during bone formation, is activated by Mg (Fleisch et al., 1968), possibly through activation of PP transphorylase (McCarty et al., 1974). In vitro inhibition of phase conversion of amorphous to crystalline $CaPO_4$ has been best effected by solutions containing both PP and Mg (Root, 1990). However, pyrophosphatase and alkaline phosphatase, the enzymes that destroy the mineralization-inhibiting enzyme, are also Mg dependent (Kunitz and Robbins, 1966; Heaton, 1980). Mineralization is favored or inhibited by Mg, depending on local conditions (Heaton, 1980). Where there is a high Ca/Mg ratio, as in bone, pyrophosphatase action dominates, preventing Mg-inhibition of apatite formation. The high Mg/Ca ratio in normal soft tissue inhibits formation of apatite, Mg complexing more effectively than Ca with ATP (Leonard et al., 1971). The formation constant ratio of MgATP/CaATP is 2.9/1. At Mg/Ca ratios of over 2 there is strong inhibition of apatite formation (Bachra and Fischer, 1969). In skeletal muscle, the ratio is 6.4 (Leonard et al., 1971), and the presence of Mg slows the precipitation and crystallization processes (Neuman and Mulryan, 1971). Thus, a subnormal Mg/Ca ratio might be an important factor in calcification of soft tissue; increasing the level of Mg might inhibit calcinosis (Granicher and Portzehl, 1964). In fact, Mg has inhibited subcutaneous calcification induced by subcutaneous injection of CaATP in rats (Leonard et al., 1972). Whether low Mg levels in the soft tissues precede the degenerative changes that progress to fibrosis, calcification and ossification in these disorders is unknown.

B. Chondrocalcinosis

Enlarged joints and stiffness were among the early findings in Mg-deficient calves (Huffman et al., 1930) and guinea pigs in which periarticular $CaPO_4$ deposits were observed (Hogan et al., 1950), especially with high PO_4 intakes (House and Hogan, 1955).

Chondrocalcinosis is a metabolic disease occurring in young children, adolescents and young adults, with deposition of Ca-PP-dihydrate crystals in and around joints, and of inorganic PP in the synovia. It was encountered first in patients with vitamin D toxicity or hyperreactivity (Howard and Meyer, 1948; Chaplin et al., 1951; Christensen et al., 1951; DeWind, 1961; review: Seelig, 1980), and then associated with renal Mg wasting (Runeberg et al., 1975; Rapado and Castrillo, 1980; Mayoux-Benhamou, 1985), with Bartter's syndrome (Bauer et al., 1979). Hypophosphatasia is another condition associated with calcification of articular cartilage, particularly in patients with osteoarthritis (Lessell and Norton, 1964; O'Duffy, 1970; McCarty et al., 1971; 1974). Hypophosphatasia has been produced experimentally in animals by Mg deficiency (Lai et al., 1975) and by hypervitaminosis D (review: Seelig, 1980).

A boy of three and a half years, whose infantile convulsions had been treated with vitamin D, developed hypercalcemia and osteochondrosis. Later identified was symptomatic hypomagnesemia, that was treated with $MgSO_4$ with some improvement (Miller, 1944). Another young boy had chondrocalcinosis associated with hypomagnesemia, that was caused by renal wasting too severe to be corrected by long-term Mg treatment; six years later he died of CMP (Klingberg, 1970; personal communication). A young man, with a history of convulsions, hypokalemia and hypocalcemia at six years of age, who had been treated with Ca and K, presented with tetanic convulsions and arthritic pain (Runeberg et al., 1975). His hypomagnesemia was detected when he was 14 years old, by which time he also had renal Mg wasting, hypercalciuria and bilateral renal calcinosis; by 16 years he had chondrocalcinosis, as well as abnormal electrocardiographic tracings. Orally administered $MgCl_2$ and $Mg(OH)_2$ were poorly absorbed. Of three additional patients with chondrocalcinosis and renal Mg wasting, two also had Mg malabsorption (Rapado and Castrillo, 1980).

C. Pseudogout
Precipitation of Ca-PP-dihydrate in synovial fluid causes pseudogout, a disease often associated with osteoarthritis and with moderate hyperparathyroidism (McCarty et al., 1974). A patient whose peptic ulcer was treated with aluminum hydroxide, who exhibited hypophosphatasia and low serum and synovial Mg levels, also developed pseudogout (Cohen and Kitzes, 1983).

D. Articular calcification of uremia
Calcification around and within joints, and in other soft tissues, that develops in uremic patients, is associated with hyperphosphatemia (review: Parfitt, 1969). "Sensitization" with vitamin D or PTH was suggested as a unifying hypothesis.

E. Interstitial and periarticular calcinosis
In calcinosis cutis, circumcripta or universalis, mineralization occurs chiefly in the skin. The dense connective tissues of the extremities is affected in interstitial calcinosis. It may involve hydroxyapatite deposition in subcutaneous tissue, in ligaments, tendons, or be periarticular (Sunderman and Sunderman, 1957; Leistyna and Hassan, 1964).

F. Myositis ossificans
In myositis ossificans, whether post-traumatic or the progressive metabolic disease termed myositis ossificans progressiva (M.O.P., or stone man disease), true bone forms in tendons and ligaments and in the fibrotic and then calcinotic involved muscle (Lutwak, 1964; Illingworth, 1971; McKusick, 1972). The lesions of M.O.P. resemble those produced by Mg deficiency in rats: degenerative changes in skeletal muscle that progress to cell infiltration, granulomatous nodules, fibroblastic proliferation and calcification (Heggtveit, 1969). Animal studies of the effect of Mg on intramuscular calcification at the site of injection of a calcergic substance (PbCl2) showed that, when injected mixed with the $PbCl_2$, Mg decreased or prevented formation of $CaPO_4$ crystals in the form of apatite, octocalcium, phosphate, and brushite (Anders et al., 1980; Anders and Flajs, 1981).

VII. SOFT TISSUE MINERALIZATION - TOXIC REACTIONS

A. Fluoride toxicity; treatment of osteoporosis
Periarticular calcification has been recognized in regions of high water content of fluoride (F) and as a complication of F treatment of osteoporosis (Anders et al., 1978). Long-term administration of F has intensified the renal calcinosis of Mg-deficient rats (Ophaug and Singer, 1976). Dyschondroplasia, with overgrowth enveloping bone, joints, and tendons, has been produced in guinea pigs on a diet high in F and low in Mg (Thompson et al., 1964). Effects of combination of F with Ca and with Mg in experimental animals have shed light on problems encountered in F treatment of osteoporosis. Rats that were both Mg and Ca deficient were given Ca, Mg, F, Ca + F or Mg + F. Rats given Ca supplements had the lowest plasma Mg and the highest renal Ca. Mg + F decreased renal Ca, as well as myocardial and arterial Ca (Ericsson et al., 1986). Mg-deficient rats fed 2% orthophosphate (such as is used to inhibit sucrose caries) increased renal calcinosis and tubular calculi in dilated tubules and Henle's loops. Added Mg partially decreased renal and arterial calcinosis (Luoma et al., 1976), and decreased $CaPO_4$ crystal formation (Anders et al., 1978).

B. Vitamin D toxicity, hyperreactivity and sarcoidosis
Since vitamin D excess causes hypercalcemia and potentiates renal and arterial calcinosis of animals on high Ca/Mg diets, it is not surprising that high dosage vitamin D treatment of adults (Danowski et al., 1945) and consumption of milk over-fortified with vitamin D and/or other sources of the vitamin by children, who were hyperreactive to vitamin D, resulted in metastatic calcinosis that involved kidneys and the CV system (vide supra).

Sarcoidosis: Hyperreactivity to vitamin D of sarcoidosis also results in visceral calcinosis (Shanks and MacDonald, 1959). Macrophages of patients with sarcoidosis have been shown to synthesize calcitriol, the metabolically active form of vitamin D (Reichel et al., 1989).

C. Phosphate treatment of hypercalcemia
Severe hypercalcemia, treated with oral phosphates (usually with other measures to lower life-threatening Ca levels) has caused metastatic calcification (Carey et al., 1968; Dudley and Blackburn, 1970; Eisenberg, 1970; review: Seelig, 1980). Such treatment has caused pulmonary, pancreatic and ocular calcification, in addition to the more usually described renal and CV involvement (Schackney and Hasson, 1967; Breuer and LeBauer, 1967).

VIII. MISCELLANEOUS MINERALIZATIONS

A. Placental calcification
Mg-deficient pregnant rats had placental calcification and bore abnormally small pups (Dancis et al., 1971). Placentas of women who had toxemias of pregnancy, the size of whose infants indicate intrauterine growth retardation, contained much more Ca and less Mg than did normal placentas (Charbon and Hoekstra, 1962). High dosage vitamin D during pregnancy has caused placental damage and calcification (Brehm, 1937).

B. Pancreatic calcification
Acute pancreatitis, from ethionine treatment of choline-deficient mice, was characterized by high pancreatic Ca and low pancreatic Mg, that was believed to contribute to the pathophysiology (Song and Adham, 1989). Induction of acute pancreatitis with bile salts in dogs and rats suggests that the hypocalcemia of acute pancreatitis may be caused by translocation of excessive Ca from the extracellular to the ic space, which is accompanied by depletion of pancreatic Mg and damage to cell membranes (Bhattacharya et al., 1985; 1988). A study to ascertain whether Mg deficiency plays a role in the pathogenesis of hypocalcemia of acute pancreatitis disclosed low serum Mg in only 6 of 29 patients, but mononuclear blood cell Mg levels were significantly lower in hypocalcemic pancreatitis patients (half the total) than in those with normal serum Ca (Ryzen and Rude, 1990). Patients with alcoholic pancreatitis, who were tested for Mg deficiency by a low-dose parenteral Mg load, showed increased Mg retention. Hypercalcemia caused by vitamin D

toxicity has been implicated in the pathogenesis of acute pancreatitis (Leeson and Fourman, 1966).

C. Ocular calcification

Among the lesions of disseminated calcification caused by hyperphosphatemia has been angioid streaks of the retina (McPhaul and Engel, 1961). Slit-lamp conjunctival examination has been recommended to detect early (conjunctival) extraskeletal calcification in patients undergoing high PO_4 treatment of hypercalcemia (Dudley and Blackburn, 1970). Scleral calcification has been seen in vitamin D toxicity (Frost et al., 1947), and band keratopathy and conjunctival calcification has been seen in patients with hypophosphatasia (Lessell and Norton, 1964), a condition that has been produced experimentally in animals by Mg deficiency (Lai et al., 1975) and by hypervitaminosis D (review: Seelig, 1980). Mg deficiency in rabbits reduced serum Mg and K levels and increased Na and Ca, which was associated with extensive pathomorphologic changes in the lens, including calcinosis (Stankiewicz et al., 1971; Knopik et al., 1973). A low Mg/Ca ratio has been found in human calcified cataractous lenses (LaPiana and Leonard, 1973). The mechanism by which changes in Mg and Ca in the eye participate in cataract formation is obscure. Ca has induced aggregation of urea-deaggregated insoluble protein derived from human lens, the rate of aggregation increasing with the degree of senescence of the lens. The aggregation was more active with cataractous than with normal lenses of the same age. A Ca-sensitive polypeptide, that precipitated out when Ca was added, was isolated from cataractous human lenses (Satoh et al., 1990)..

IX. TREATMENT OF ABNORMAL CALCIFICATION

A. Cardiovascular

Numerous animal studies have shown that increasing Mg intake protects against arterial and cardiac damage and calcification. Epidemiologic evidence supports the premise that life-long low Mg intakes and conditions that cause hypercalcemia contribute to cardiovascular disease (Seelig and Heggtveit, 1974; Seelig, 1980). However, definitive clinical proof, i.e. from extensive intervention studies, is not yet available.

B. Uroliths

The efficacy of raising the urinary output of Mg and decreasing that of Ca has been repeatedly demonstrated, both in animals and humans. Mg deficiency need not be manifest for prophylaxis with Mg salts to be effective (Moore and Bunce, 1964; Oreopoulos et al., 1968; Melnick et al., 1971; Johansson, 1979; 1986; Johansson et al., 1981; Hradec, 1989). As indicated above, many factors influence formation of stones, and there is not uniformity of opinion as to the efficacy of treatment modalities: Mg alone or with pyridoxine to decrease oxalate formation (Prien, 1965; Gershoff and Prien, 1967), or agents such as diuretics that increase the urinary Mg/Ca ratio (Johansson et al., 1983). A recent study suggests that the efficacy of Mg and citrate is increased by taking them with meals (Lindberg et al., 1990).

C. Ectopic soft tissue calcification

Treatment of soft tissue calcification by restriction of Ca and/or vitamin D intake and by Ca-chelation therapy has been minimally helpful (Klein and Harris, 1955; Davis and Moe, 1959; Lutwak, 1964; Geho and Whiteside, 1973; Rabens and Bethune, 1975). Diphosphonates were shown to inhibit formation of $CaPO_4$ crystals in vitro and pathological calcification in vivo (Francis et al., 1969) and have been used with somewhat better success in humans (Geho and Whiteside, 1973; Smith, 1975; Hentzer and Jacobsen, 1978), in conjunction with osteolysis-inhibitors and calcitonin when there is hypercalcemia, i.e. from metastatic neoplasms or from high vitamin D levels as in sarcoidosis (Attie, 1989).

Treatment with large enough doses of Mg to compensate for its renal wastage (i.e. in chondrocalcinosis) has resulted in clinical improvement. Reversal of the calcinosis might be mediated by solubilization of inorganic PP, and inhibition of its formation by increased Mg. It was effective in a patient who had been ineffectively treated for three and a half years

with diphosphonates (Anders et al., 1985). Another patient whose diphosphonate treatment was delayed because of his existing osteopenia - diphosphonates having caused bone demineralization in other M.O.P patients (Rogers et al., 1977) - had it added to the highest tolerable oral doses of Mg, after a year of Mg treatment alone (Seelig et al., 1985). This patient's calcinosis cutis of his face gradually softened - permitting him to open his mouth fully to eat normally and to receive needed dental treatment, rather than only enough to admit a straw. The calcinosis of the muscles of his extremities and that of his paravertebral muscles also softened sufficiently to permit him to sit in and maneuver a motorized wheelchair. In addition, his moderately high PTH levels were lowered and his calcitonin levels were elevated. Ossification of ligaments and tendons was unchanged.

In a long-term study of 80 patients with ectopic calcification and ossification, Mg treatment inhibited $CaPO_4$ precipitation both by local injection of $MgSO_4$ with a local anesthetic into the calcified area for 2-20 weeks, and by oral administration of Mg lactate for 4-6 months. Diminution to complete disappearance of calcific deposits was observed in all cases. In most, some mobility of involved joints was restored. Mg prevented further ectopic calcification. Mg arrested ossification and may have induced some resorption of immature bone. Patients included 24 with myositis ossificans traumatica, 23 with calcific bursitis, 6 with para-osteoarthropathy of elbow after craniocerebral injuries, 9 with periarticular calcification after local trauma, 13 with postoperative calcifications of the hip joint, and 5 with calcifications at insertions of tendons and ligaments (Ditmar and Steidl, 1989; Steidl and Ditmar, 1990).

X. CONCLUDING COMMENTS

Pathological mineralization - predominantly by Ca compounds - can be limited to the CV or urinary system, can involve both, or can occur - usually as part of a metastatic calcification process - in the pancreas and/or lungs, and even in eyes. These tissues have been reported to be calcified in the presence of Mg deficiency, often contributed to by hypercalcemia. The soft tissue calcinoses and ossification, except for chondrocalcinosis which may be a complication of renal Mg wasting associated with nephrocalcinosis, are neither associated with hypercalcemia nor overt Mg deficiency. The animal and epidemiologic data suggest that Mg treatment of arteriosclerosis, renal calcinosis and urolithiasis should probably be prophylactic. Suitable intervention studies are still needed to determine whether the still major killer in the developed world: ischemic heart disease and strokes, might be diminished by increasing Mg intake. Calcareous kidney stone formation is favorably influenced by increasing Mg intake, and even the most devastating of the soft tissue mineralizing diseases, M.O.P., seems to respond to Mg treatment.

Abbreviations

ADP = adenosine diphosphate; ATP = adenosine triphosphate;
CMP = cardiomyopathy; CV = cardiovascular;
MI = myocardial infarction;
M.O.P. = myositis ossificans progressiva; PTH = parathyroid hormone

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Chapter 5: Metal Ion Deposits and Disease

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