Magnesium and the Arteries: I. Effects of Magnesium Deficiency on Arteries and on the Retention of Sodium, Potassium, and Calcium

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INTRODUCTION

Experimental data demonstrate that magnesium (Mg) deficiency causes arterial damage and dysfunction. Models of Mg deficiency, in which the vasculature is examined, show arterial lesions that resemble the earliest signs of human arteriosclerosis. The nature of the more advanced experimental lesions of Mg deficiency depends upon concurrent cardiopathic or arteriopathic challenges: dietary, electrolyte, hormonal, drug, or stress. Excesses of cations, the retention of which is caused by Mg deficiency (Ca and Na)), intensify the lesions; (K), the retention of which is interfered with by Mg deficiency, is protective. Hormones, phosphates (PO_4), or drugs that adversely affect Ca or Mg distribution, intensify the vascular lesions. These and other modalities, employed to damage the cardiovascular (CV) system, are more toxic in the presence of Mg deficiency; prior or concomitant Mg administration is protective. Many of cardiovasopathic experimental models are representative of challenges to which man is subject in the industrialized world: 1) excessive fat, salt, PO_4, protein, vitamin D, and often Ca, in the face of marginal Mg intake; 2) excess catecholamines and corticosteroids (the release of which is triggered by stress); and 3) use of magnesiuretic agents, such as alcohol, diuretics, or mineralocorticoids (MCS). Most of these agents increase Mg requirements and intensify Mg deficiency.

The CV lesions of experimental Mg deficiency (infra vide) are similar to those seen in arteriosclerosis of infants and children, in that they usually entail fibroblastic intimal proliferation and degeneration of the internal elastica and focal degeneration of the tunica media, generally of the small coronary arteries (infra vide). Low Mg levels have been reported, not only in infancy but also during pregnancy. Magnesium deficiency under these conditions might contribute to the earliest signs of arteriosclerosis, which include splitting or fragmentation of the internal elastica and intimal thickening. Plaque formation usually is not seen until later in the course of the disease, and may reflect superimposition of such factors as high fat or vitamin D intakes. Possibly, the significance of the lower incidence of sudden death from ischemic heart disease (IHD) in hard as opposed to soft water areas relates to protection derived from the Mg in hard water counteracting both the pediatric origin of arterial disease and its fatal expression (triggered by arrhythmia or infarction), as well as chronic morbidity.

The electrolyte abnormalities produced by Mg deficiency: low Mg and K, and high Ca and Na (changes that are more marked in the tissues than in the serum), may predispose to changes in arterial resistance to blood flow (see Part II, this Symposium).

ARTERIAL DAMAGE OF EXPERIMENTAL MAGNESIUM DEFICIENCY

To obtain insight into the nature of the abnormalities in the CV system that are caused by Mg deficiency or loss, it is necessary to evaluate findings from a wide variety of experimental models. Arterial changes and mineral retention have been studied in many species; the effects of Mg restriction and administration have been evaluated against a background of dietary imbalances, hormonal and drug challenges, and stress. Most of the studies of the effects of Mg on the CV system were designed to produce damage by high fat and cholesterol intakes, by loading with Ca, or by NaH_2PO_4 , or by specific cardiotoxic agents. Since most of these challenges cause egress of Mg, and subsequently of K, from the soft tissues, and retention of Na and Ca (effects that are produced by Mg deficiency alone), the findings are applicable to an evaluation of the role of Mg in the CV system.

Experimental Magnesium Deficiency with Otherwise Balanced Diet

There are few experimental studies of the vascular changes caused by Mg deficiency alone (see Table 1). Lowenhaupt et al. (1950) reported that young rats kept on a normal diet, except for Mg deficiency, developed perivascular myocardial infiltration with macrophages and lymphocytes, and necrosis. The myocardial lesions were seen (within 2 weeks) around the small coronary radicals of precapillary and capillary size. The lesions of surviving animals evolved through stages of fibroblastic proliferation and fibrous healing. Comparable focal areas of pericapillary myocardial infiltration and necrosis, with lipid droplets and collagen fibrils were reported in rats on Mg-low, otherwise balanced, diets (Mishra, 1960a, Mishra and Herman, 1960). Seta et al. (1965), as part of their study of concomitant K and Mg deficiency in rats, found that myocardial and plasma K dropped and myocardial Na rose, even when there was a deficiency only of Mg. The cardiac lesions, seen in doubly deficient and Mg deficient rats, were patchy with combinations of myocytolysis, edema, and infiltration with mononuclear and neutrophilic cells. Only when the Mg-deficient rats were stressed, did they show increased cardiac Ca. Although no arterial histologic findings were reported, the perivascular myocardial lesions suggest that there may have been abnormalities. Hungerford and Bernick (this symposium), provide details of the coronary arterial damage in Mg-deficient rats: intimal cell damage, edema and hyperplasia, internal elastica fragmentation, and medial hyperplasia. In guinea pigs on Mg-deficient, but otherwise normal diets, no histologic data were given however myocardial and skeletal muscle Na and Ca were elevated and K lowered, with no significant change in serum electrolytes, other than low Mg (Grace and O'Dell, 1970a,b). Dogs on otherwise balanced Mg-deficient diets showed both perivascular myocardial necrosis and edema (Unglaub et al., 1959; Wener et al., 1964). The small coronary arteries and arterioles showed pyknotic intimal cells, but no intimal hyperplasia; their medial muscle cells were loosely arranged, suggestive of edema, with necrosis and inflammation. The larger coronaries were less damaged (Wener et al., 1964). Also seen, were

slightly increased serum Na and peripheral edema (Wener et al., 1964) and decreased serum Ca (Unglaub et al., 1959; Bunce et al., 1962b; Featherston et al., 1963; Wener et al., 1964), despite which intimal and medial calcification developed (Syllm-Rapoport and Strassburger, 1958; Bunce et al., 1962b; Featherston et al., 1963; Morris et al., 1963). Large myocardial infarcts (MI) were seen in severely Mg-deficient dogs (Morris et al., 1963). Supplementation of the basal (Mg-deficient, otherwise adquate) diet with 320 ppm of Mg, raised the serum Mg from 0.89 to 1.89 mg % and the serum Ca from 7.88 to 11.3 mg %, although concomitantly it lowered the Ca content of the aorta tenfold (from 1076 mg % in the Mg-deficient dogs to 116 mg % (Featherston et al., 1963)). Endocardial fibrosis and pulmonary emboli were seen in Mg-deficient dogs that were also found to exhibit increased plasma renin activity and urinary aldosterone (El Shahawy, 1971).

Table 1. Coronary Arterial and Cardiac Lesions: "Pure" Magnesium Deficiency

CORONARY ARTERIES		CARDIAC	
INTIMA a,b	EDEMA HYPERTROPHY HYPERPLASIA ±CALCIFIED PLAQUES	MYOCARDIAL[e] PERIVASCULAR[a]	INFILTRATION EDEMA NECROSIS
INTERNAL ELASTICA b,c,e	THINNING FRAGMENTATION LIPID DROPLETS ± CALCIFICATION*		FIBROSIS[a]
		VALVULAR MALFORMATIONS[e]	
MEDIA c,e	EDEMA NECROSIS HYPERPLASIA	ENDOCARDIAL FIBROSIS[d]	

Demonstrated in rats (Lowenhaupt et al(1950)[a], Mishra & Herman (1970)[a], Seta et al (1965)[a], Hungerford & Bernick(this symp.)[b]. In dogs (Unglaub et al (1959)[c], Wener et al(1964), Morris et al(1963)[c], El Shahaway (1971)[d]. In cows (Arnold (1960)[e], Lynd et al (1965), Willers et al (1965)[e].

*Calcification with moderately high dietary Ca; 10-fold decreased arterial Ca with increased dietary Mg (Featherston et al (1963)).

It was in cows, on spring forage on Mg-poor soil, or where other factors interfered with the availability of Mg, that the histologic arterial changes of Mg deficiency were first characterized (Arnold and Fincham, 1950) and reaffirmed in controlled studies (Lynd et al., 1965; Willers et al., 1965). The coronary arteries and the endocardium showed intimal thickening and subendothelial degeneration and calcification of elastica fibers. Medial calcification and calcific intimal plaques were also described, as were valvular malformations and myocardial infarcts (Willers et al., 1965). The syndrome, leading to these CV lesions, was seen predominantly in lactating cows in areas where "grass tetany" or convulsions of Mg deficiency (characterized by hypomagnesemia and hypocalcemia) occurred during late pregnancy or during lactation. Not only cows, but ewes, are susceptible to this disorder, and it has been noted that it is more prevalent in herds with a high incidence of toxemia of

pregnancy (Herd, 1966).

Experimental Magnesium Deficiency with High Calcium and/or Vitamin D

Calves fed whole milk, usually supplemented with vitamin D, or a comparable synthetic diet low in Mg, for prolonged periods, developed neuromuscular signs of Mg deficiency and endocardial and intimal plaques, degeneration, fragmentation, and calcification of the elastic fibers of both endocardium and arteries, focal myocardial necrosis, and phlebothrombosis (Moore et al., 1936, 1938; Blaxter et al., 1954 (see Table 2). The syndrome was preventable by supplementation with 30-40 mg/kg/day of Mg (Duncan et al., 1935; Huffman and Duncan, 1936; Blaxter et al., 1954). Despite these calves' high Ca intakes, their serum Ca remained normal or slightly low. In addition to the endocardial and intimal calcification, calves on a whole milk diet developed high serum cholesterol levels (Thomas, 1959).

Rats have long been considered unique in that Mg deficiency has caused hypercalcemia rather than the hypocalcemia reported in other species. Larvor (1971) has tabulated the Mg, Ca, and vitamin D intakes of rats on diets designed to produce Mg deficiency, and has shown that the extent of their hypercalcemia seemed to depend, not only on the degree of Mg deprivation, but on the simultaneous Ca and vitamin D loads. The Ca/Mg ratios were as high as 500/1. They also had 500-1000 U vitamin D mixed into each kg of their diet. Nonetheless, those with Mg intakes above 60 ppm/day usually did not develop marked hypercalcemia. Neither did it develop in rats without exogenous vitamin D (Lifshitz et al., 1967). Maynard et al. (1958) showed, in guinea pigs, that much of the damage of low Mg intake results from the abnormal Ca/Mg and phosphorus (P)/Mg ratios, caused by lowering the Mg and leaving the diet relatively high in Ca and/or P. It is important to remember that high intakes of Ca or P interfere with the intestinal absorption and may result in greater renal excretion of Mg, and that high intakes of vitamin D also favor retention of Ca over that of Mg (for review see Seelig(1971,1980)

Cardiovascular changes, similar to those seen in "pure" Mg deficiency, developed in rats fed 400-650 times as much as Ca as Mg (versus 40/1 in controls, which is also a higher than normal Ca/Mg ratio). There were small inflammatory and necrotic myocardial lesions, with increased tissue Ca and Na, but no significant change in serum Ca, and low tissue and serum Mg and K (Mishra, 1960a; Ko et al., 1962). Adding sufficient Mg to lower the Ca/Mg ratio to 3/1 prevented the lesions (Mishra, 1960a). In a study designed to show how much Mg is necessary to prevent macroscopically manifest intimal calcific plaques in dogs on Ca/Mg intakes of 33 to 50/1, Bunce et al. (1962a) found that 180 ppm of Mg prevented grossly visible aortic intimal lesions in all seven dogs receiving 0.6% of Ca (Ca/Mg=33/1). Most of the dogs getting only 80 ppm Mg had intimal plaques, whether their Ca intakes were 3000 (Ca/Mg=35/1) or 6000 ppm (Ca/Mg=50/1). Serum Ca levels were highest (11.7 mg%) in the dogs on the highest Mg intake (180 ppm), and only 8.8 mg% in dogs getting the highest Ca/Mg dietary ratio (9900 ppm Ca/80 ppm Mg, or 100/1).

Since vitamin D normally increases serum Ca levels and increases Mg requirements (Seelig, 1971), it is of interest that Mg-deficienct dogs on normal Ca intakes showed minimal coronary arterial calcification unless they were given vitamin D or an intravenous (i.v.) Ca load (Syllm-Rapoport and Strassburger, 1958; Unglaub et al., 1959). An early study (Handovsky and Goormaghtigh, 1935) showed that moderately high doses of vitamin D significantly raised the blood pressure in dogs; that vitamin

Table 2. CARDIOVASCULAR LESIONS OF DIETS LOW IN MAGNESIUM AND HIGH IN VITAMIN D[a] AND CALCIUM (WHICH INTERFERE WITH MAGNESIUM RETENTION)

Coronary Arteries and Endocardium	Myocardium	Species	Investigators
Intimal and Endocardial Plaques Elastica Fragmentation Calcification Fibrosis	Focal Necrosis Perivascular Micro-and Macrofocal Calcification Inflammation	Calves	Moore et al (1936, 1938) Blaxter et al (1954)
		Rats[b]	Larvor (1971/1973) Mishra (1960a) Ko et al (1962) Sos et al (1960); Sos (1965)
Phlebothrombosis			
Arteriosclerosis Calcification of Aorta High Blood Pressure		Rats	Rigo et al (1965a,b)
Arterial Calcification Intimal Plaques (Aorta)	?	Dogs	Syllm-Rapoport & Strassburger (1958) Unglaub et al (1959) Bunce et al (1962 a,b)

a. Hypervitaminosis D leads to increased blood pressure and blood lipids; arteriosclerosis. These changes are prevented by magnesium intakes higher than normal — Sos (1965); Rigo et al (1965a,b)

b. Hypercalcemia of magnesium deficiency in rats is related to high Ca/Mg dietary ration (500/1) and high vitamin D intakes — Larvor (1971)

D excess causes arteriosclerosis has been known even longer (Kreitmair and Moll, 1928). The variation in susceptibility to vitamin D toxicity in rats was recognized in 1930 (Duguid, 1930) and more intensively studied in 1956 (Gillman and Gilbert, 1956). Like the arterial lesions of Mg deficiency, those of hypervitaminosis D involved medial and elastica degeneration and calcification (Seelig, 1969), but the predominant lesions described were of the larger arteries, rather than of the coronaries. Rats on toxic doses of vitamin D also developed hypercholesterolemia, hypertension, and aortic calcification; the latter changes were prevented by high dosage Mg supplementation (Sos et al., 1960; Rigo et al., 1965a,b; Sos, 1965).

Experimental Magnesium Deficient, High Fat Diet

In studies of the influence of Mg deficiency and its repletion on the development of atherosclerosis in rats fed a number of combinations of saturated or unsaturated fat diets with and without added cholestesterol, cholic acid, and Ca, Vitale and his colleagues showed dissociation between serum and arterial lipids (Seelig and Vitale, 1973) (see Table 3). Under dietary conditions that increased serum cholesterol levels, high Mg intakes resulted either in no change in serum cholesterol, or in an actual rise; serum lipoproteins fell, as did the arterial lipid deposition. High Ca intake (in the presence of low Mg intake) lowered serum lipids slightly, but increased arterial lipids (Hellerstein et al., 1957; Vitale et al., 1957, 1959; Hellerstein et al., 1960; Nakamura et al., 1960). Long-term Mg administration to rats on atherogenic diets produced an early increase in serum lipids that fell only gradually within the year-long observation, but a significant decrease in arterial lipid deposition was evident within 2 months on the Mg-supplemented diet (Nakamura et al., 1960, 1966). The rats on the low Mg, high fat diet exhibited subintimal and medial degeneration and calcification of the elastica, as well as intimal atheromata (Nakamura et al., 1966). Hungerford and Bernick (this symposium) show that organized endothelial plaques develop in Mg-deficient rats on high cholesterol intake, but not with Mg deficiency alone.

Studies of the effects of Mg deficiency and supplementation in rabbits on atherogenic diets also showed that Mg supplementation influenced the serum cholesterol only slightly, although it tended to decrease atheroma formation (McCann et al., 1962; Neal and Neal, 1962; Nakamura et al., 1965; Hirano, 1966; Lacson et al., 1966; Wartman et al., 1967). In one of the studies, in which elevated intimal plaques, fragmented and calcified elastica, and mural thrombi were reported in the Mg-deficient rabbits, the matched cholesterol-loaded, Mg-supplemented rabbits showed no calcified lesions and less foam cells in the subintimal layer of the aorta. Narrowing of the coronary artery was noted in all of the cholesterol-loaded rabbits, but to a somewhat lesser degree in the rabbits on high Mg intakes. Greater involvement of the small coronary arteries is suggested by the microscopic foci of myocardial necrosis in half the rabbits on Mg-deficient, high cholesterol diets, but in none of those that were Mg-supplemented.

The early Mg deficiency studies were in dogs on diets high in saturated fats (Kruse et al., 1933, 1934); those dogs had "fat clots" in their blood. They showed no alteration in total serum lipids but had an increase in total cholesterol, most of which was in the esterified fraction. The fatty acids increased early during Mg deprivation, but fell during the fourth week on the deficient diet. Bunce et al. (1962a)

Table 3. Cardiovascular Lesions of Low Magnesium Diet High in Fats (Which Decrease Magnesium Absorption; Increase Need)

Arteries	Myocardium	Species	Investigator
Atheromata[a]		Rats	Vitale et al (1957, 1959)
Subintimal Degeneration	?	Rats	Hellerstein et al (1957, 1960)
Medial Degeneration		Rats	Nakamura et al (1960, 1966)
Endothelial Plaques		Rats	Hungerford & Bernick (this Sympos.)
Atheromata[a]		Rabbits	Neal & Neal (1962); McCann et al (1962)
Coronary Arteries Narrowed[a]	Microscopic Necrotic Foci	Rabbits	Lacson et al(1966); Hirano et al (1966)
Elastica Fragmentation; Calcification		Rabbits	Nakamura et al(1965); Wartman et al(1967)
Intimal Plaques & Thickening		Dogs	Bunce et al (1962a,b); Vitale et al(1961)
Artheromata[a] Intimal Fibroblastic Thickening Elastica Fragmentation		Monkeys	Vitale et al (1963)

a Lesions intensified by Mg deficiency; protected against by Mg supplements

showed that increasing the Mg intake, sufficiently to prevent intimal lesions in dogs on a high saturated fat diet, increased their serum cholesterol levels (to 340 mg %), whereas the dogs on the highest Ca/Mg ratio had lower serum cholesterol levels, but had gross intimal plaques. Dogs on a Mg-free, corn oil-rich, low Ca diet had intimal thickening and plaques with narrowed arterial lumens, but minimal lipid deposition (Vitale et al., 1961). Monkeys on a similar diet exhibited raised intimal atheromata and fibroblastic intimal thickening, with disrupted elastica, but no arterial calcification. The Mg-deficient monkeys had significantly higher serum cholesterol levels than did the controls (Vitale et al., 1963).

Rayssiguier and Larvor (this symposium) have correlated cold stress (which Heroux et al. (1973) have shown to intensify the cardiac damage of Mg deficiency) with epinephrine- or theophylline-induced lipolysis, increased serum fatty acids, and hypomagnesemia.

Experimental Cardiovasopathic, Infarctoid Diets

A combination of low Mg (about one third the daily requirement) and low KCl intake, plus high fat, protein, vitamin D, Na, PO_4, and cholesterol, but normal Ca intake, resulted in the development of spontaneous MI and hypertension in rats, cocks, and dogs (Sos et al., 1960, 1964a, b, c; Sos, 1965; Rigo et al., 1961, 1963a,b; Gati et al., 1964, 1965; Rigo, 1965; Rigo et al., 1965a,b; Rigo, 1971; Szelenyi,1971, 1973) (see Table 4). Elimination of cholesterol from the cardiovasopathic (CVP) diet lowered the serum cholesterol from 573 to 211 (vs. 94 in controls on normal diets), had no effect on the hypertension, and decreased the incidence of MI from 90 to 60% of the group. Lowering the protein intake from almost twice normal to normal, resulted in a further rise in serum cholesterol (to 637), no significant change in hypertension, but a further reduction in incidence of MI to 40% of the experimental group. Providing a normal salt mixture influenced neither the hypercholesterolemia nor the hypertension, but lowered the incidence of MI to 13%. The rats on the CVP diet retained 15 times as much Na as did the controls, but their myocardial and serum Na levels differed little from control values. Their myocardial Ca rose 12%, but their serum Ca remained essentially unchanged. Their myocardial Mg and K levels dropped 19 and 33%, respectively; serum values of both cations dropped about 20% (Sos, 1965). Increasing the dietary intake of $MgCl_2$ fivefold over the normal requirement mitigated, significantly, the cardiopathic changes as well as the coronary and aortic pathology, which had included thickening of the small coronary arteries, with marked increase of the arterial wall/lumen ratio (Sos, 1965; Szelenyi, 1973b). The increased Mg intake also reduced the extent of damage produced by such intensifying factors (added to the CVP diet) as neurogenic stress, or ACTH. When the CVP diet was modified by increasing the cholesterol threefold, the fat fourfold, vitamin D_2 and cod liver oil one third each, and thiouracil, marked hypercoagulability was produced. Fivefold increased Mg intake restored the coagulation and prothrombin times to normal (Szelenyi, 1971, 1973).

Other Cardiovasopathic Models

Arterial lesions, similar to those produced by Mg deficiency in combination with a high Ca or vitamin D intake, have been produced by

modalities that increase serum Ca or cholesterol levels, increase Na retention, and decrease Mg and K, both in the serum and in the tissues. (see Table 5.) Dihydrotachysterol, particularly in combination with NaH_2PO_4, causes calcification of the aorta and coronary arteries, as well as periarteritis; the lesions are intensified by deficiency of Mg or K; administration of each protects against the lesions (Selye, 1958 a,b; Bajusz and Selye, 1959; Mishra, 1960c). Mineralocorticords, plus PO_4 produce multifocal necrosis, the intensity of which is increased by Mg and/or K deficiency; each cation is protective (Selye, 1958a,d,f; Selye and Mishra, 1958; Bajusz and Selye, 1959; Mishra, 1960b; Selye and Gabbiani, 1965). Parathyroid (PT) extract, with NaH_2PO_4 (Selye, 1958c; Lehr, 1963) or stimulation of PT secretion and/or adrenal medullary and cortical secretion, as occurs in renal damage or nephrectomy (Lehr, 1959), causes subintimal arterial damage with calcification of the damaged elastica, in addition to myocardial infiltration and edema.

Table 4. Cardiovasopathic Diet (CVP)

Low in: Magnesium, Potassium, Chloride	High in: Saturated fat, Cholesterol, Protein, Vitamin D, Sodium, Phosphate
Normal Calcium	

(DEMONSTRATED IN COCKS, RATS, DOGS)

Arterial Lesions	Spontaneous Myocardial infarcts
Atherosclerosis	
Calcification	
↓Lumen; ↑Wall/Lumen ratio	↑ Blood Coagulability
↓Elasticity	

Serum and myocardial electrolytes of CVP and Control diets

	Serum				Myocardium			
	Mg	K	Ca	Na	Mg	K	Ca	Na
Control	2.5	8.1	4.8	133	14.5	63	4.7	52
CVP Diet	2.0	6.6	5.0	134	11.7	42	5.5	61

Serum cholesterol, blood-pressure and incidence of infarcts. (Effects of modifying CVP diet.)

	Serum cholesterol	Blood pressure	Incidence of MI
Control	94	112	0
CVP diet	↑5-6x	↑about 50+mm	80-90%
CVP minus cholesterol	↓to<50%,CVP	No change, CVP	↓ to 60%
CVP minus Vitamin D	No change,CVP	↓about 30mm CVP	↓ to 40%
CVP with normal salts	↓ to<50%,CVP	±↑over CVP	↓ to 13%
CVPwith normal protein	↑ to 15%>CVP	No change,CVP	↓ to 40%
CVP plus 5x ↑Mg	a	a	protection

a Some studies show increased Mg leads to increased cholesterol and decreased β/α ratio(lipoproteins); Sos et al (1960, 1964a,b); Rigo et al (1961, 1963, 1965, 1971/1973a,b); Gati et al (1964, 1965; Szelenyi, 1971, 1971/1973).

Table 5. Cardiovasopathic Experimental Models that Cause Myocardial Magnesium Loss (± Magnesium Deficiency)[a]

Experimental Model	Arterial Damage	Cardiac Damage	Other Changes	Investigators
Calcemic:	Thickening: intima,		↑ Blood pressure	Moore et al (1936, 1938)
$>Ca \pm PO_4$; $>PO_4 + Na$	subintima, media		Osteosclerosis;	Syllm-Rapoport & Strassurger (1950)
	Degeneration of		Osteopenia	Selye (a958 a-f)
Dihydrotachysterol	elastica	Endocardial	Renal calcinosis	Bajusz & Selye (1960, 1961 d)
	Calcification	Valvular	↑ Blood lipids	Ko et al(1962), Bunce et al(1962a,b)
> Vitamin D	Lipids, atheroma			
Hormonal				
↑PTH 2° to:	Thickening	Necrosis:	Osteopenia	Selye (1958a,b)
-Mg or Ca deficency		Myocardial		Lehr (1959, 1963)
-Renal damage	Degeneration	+ Calcinosis		
-Exogenous PTH	(as above)			
+ Na, PO_4 load				
$PT_x + Na + PO_4$	Microcirculation	Microfocal	Renal damage	Lehr (1965a, b)
↑ CS (MCS)	involved	Myocardial	↑ Blood pressure	Selye (1958a-f), Selye & Mishra (1958)
+ Na, PO_4	predominantly	Necrosis		Selye & Gabbiani (1965)
↑ Catecholamines			Above + ↑ Lipids	Bajusz & Selye(1959, 1960)
-Stress-induced		Necrosis		Shimamoto et al (1959)
-Exogenous		Massive		Lehr et al (1966, 1969)
↑ Catecholamines	Intensification	Necrosis		Guideri et al (1971), Lehr (this volume)
+ MCS + aminophylline	of			
+ aminophylline	above			
Myocardial Hypoxia				Hochrein (1966), Hochrein & Lossnitzer(1969)
-asphyxia		Myocardial:		Cummings (1960), Bajusz & Selye (1960)
-overload		Mitochondrial		Jennings et al (1964)
-coronary ligation		damage		Rigo et al (1966)
		Necrosis		

a: Protected against by magnesium administration

Administration of MCS markedly intensifies the described CV lesions (Lehr, 1959) and those of catecholamine myocardial necrosis (Guideri et al., 1974). Paradoxically, despite the Ca-mobilizing effect of parathyroid hormone (PTH), and the vitamin D-like arterial damage it produces in combination with a PO_4 salt, Lehr (1959) has shown that PO_4-loading of parthyroidectomized (PT_x) rats causes even more severe CV lesions. Subsequent work from his laboratories has demonstrated that the common denominator in the experimental models: Ca- or PO_4-loading in the presence or absence of PTH, or with MCS, or catecholamine (exogenous or endogenous) is depletion of myocardial Mg and subsequently of K. Lehr et al. (this symposium) have shown that loss of myocardial Mg can serve as a useful index of pharmacologically induced myocardial injury, in lieu of histological evaluation. The increase of cellular Ca reflects, predominantly, the calcification of injured tissues, even in the presence of hypocalcemia (i.e., of the PT_x rat). Increased myocardial Ca, following catecholamines, is also a manifestation of their mode of action: their positive inotropic effect being mediated by the increased Ca uptake (Nayler, 1967; Reuter, 1974). Note should be taken here, that myocardial and arterial calcification is also seen in Mg-deficient animals that are normocalcemic or even hypocalcemic.

Increased catecholamine release, as a result of stress, has been associated with markedly increased myocardial damage when the aminals are Mg deficient (Bajusz and Selye, 1959; Mishra, 1960d; Bajusz, 1965a), and Mg administration has protected against stress and exogenous catecholamine-induced CV damage (Selye, 1958f; Selye and Mishra, 1958; Shimamoto et al., 1959; Mishra, 1960d; Bajusz, 1965a). Lehr and his coworkers (Lehr et al., 1966; Lehr, 1969) have shown that exogenous catecholamines decrease myocardial Mg and K and increase myocardial Ca and Na, but cause little change in the serum electrolytes. Raab et al. (1968) found similar electrolyte changes in rats stressed by prolonged isolation. As in the case of Mg deficiency-induced MCS secretion, there is evidence that Mg deficiency increases release of catecholamines: both from the adrenal medullary granules (Douglas and Rubin, 1963; Burn and Gibbons, 1964; Douglas and Rubin, 1964) and within the myocardium (Johnson, 1965). These findings support the postulate that neurohormonal-electrolyte interrelationships increase the susceptibility of the myocardium to the relative hypoxia that occurs with stress: the increased oxygen demand, caused by the increased catecholamine level in the heart, that may not be able to be met, because of the reduced capacity of the sclerotic arteries to dilate (Bajusz, 1963; Bajusz and Jasmin, 1964; Bajusz, 1965a,b; Lehr et al., 1966; Raab, 1969; Selye, 1969). Perhaps central to the metabolic abnormality of the myocardium, causing its reduced capacity to withstand relative anoxia, is cellular loss of Mg and K. Depletion of intracellular (i.c.) functional Mg, with secondary K loss (Seelig, 1972a) can result from absolute or relative dietary deficiency, such as can develop with vitamin D, PO_4 or Ca excess, fat or sugar loading, diabetes mellitus, catecholamine or MCS excess, PTH excess or lack (with NaH_2PO_4 load), hypoxia, stress, and aging (Seelig, 1972b; Seelig and Heggtveit, 1974).

The microfocal myocardial necrosis, seen in most of the drug- and stress-related experimental models, resembles the lesions of hypomagnesemic animals without a high Ca/Mg ratio. Lehr (1964 , 1965a,b, 1966) has correlated these changes with damage to the cardiac microcirculation, with medial degeneration and perivascular myocardial necrosis, and has stressed the depletion of i.c. Mg as an early and consistent change (Lehr et al., this symposium). The animals that are loaded with

Ca, vitamin D and/or fat (all agents that cause hypercholesterolemia, hypertension, or thrombogenesis) seem to have a greater tendency to develop infarcts (supra vide: CVP Diets). That Mg deficiency predisposes to hypercoagulability, and that Mg administration has been protective (Durlach, 1967), may relate to the effect of Mg on platelet function (Elin, this symposium), as well as to the effects of Mg on coagulation factors (Szelenyi et al., 1967; Stevenson and Yoder, 1972; Szelenyi, 1971, 1973; Seelig and Heggtveit, 1974).

Myocardial hypoxia, secondary to coronary artery ligation, asphyxia, or overload (Cummings, 1960; Jennings et al., 1964; Hochrein, 1966; Rigo et al., 1966; Hochrein and Lossnitzer, 1969; Jennings, 1969; Jennings and Shen, 1972; Sikka et al., 1973), is also associated with myocardial loss of Mg and K and increase of Na and Ca. Magnesium is protective (Bajusz and Selye, 1960; Rigo et al., 1966; Hochrein and Lossnitzer, 1969; Seelig, 1972b; Seelig and Heggtveit, 1974). These models duplicate the clinical observations in human infarcted myocardium (Iseri et al., 1952; Raab, 1969; Heggtveit et al., 1969; Seelig, 1972b; Seelig and Heggtveit, 1974) and in temporarily arrested heart during cardiac surgery (Singh et al., 1971/1972). Such events are associated with stress, which in turn leads to increased release of adrenal hormones: both medullary and cortical. Thus, it is provocative that both corticoids and catecholamines cause loss of Mg and K and retention of Na. That MCS hypersecretion causes such changes was first observed clinically (Mader and Iseri, 1955; Milne et al., 1957; Horton and Biglieri, 1962). Animal studies confirmed these effects: aldosterone administration caused markedly negative Mg balance, with increased Mg excretion in urine and feces and decreased muscle Mg and increased muscle Ca in rats (Hanna and MacIntyre, 1960). Subsequently it was shown that the major effect of the MCS on Mg is on its intestinal absorption and cellular uptake (Ross and Care, 1962), rather than by interference with its renal tubular reabsorption (Care and Ross, 1963). Massry et al. (1968) and Massry and Coburn (1973) have elucidated the effect of MCS on renal handling of Mg, showing that short-term administration of MCS exerts little effect on renal excretion of Mg or Ca, whereas long-term effects are significant. As the MCS increase Na retention, with expansion of the interstitial and i.c. space, the renal outputs of Mg and Ca rise. That a vicious cycle can thereby be established, is suggested by the evidence that Mg deficiency causes adrenal cortical changes (Mishra, 1960a; Larvor et al., 1964; Elin et al., 1970) with increased zona glomerulosa (Cantin, 1970) and increased aldosterone secretion (Ginn et al., 1967; El Shahawy, 1971).

SIMILARITY OF EARLY ARTERIOSCLEROTIC LESIONS IN MAN TO THOSE OF MAGNESIUM DEFICIENCY: PATHOLOGIC AND EPIDEMIOLOGIC DATA

Generalized and Coronary Arteriosclerosis and Endocardial Fibroelastosis of Infancy; Correlation with Possible Magnesium Deficiency

Arteriosclerosis, characterized by intimal fibrous proliferation and degeneration and calcification of the elastica (sometimes generalized, but more often of the coronaries) has been observed in infants who died suddenly from IHD. (see Table 6). Such fatalities in infancy and childhood have led to reviews of the literature and studies of autopsy material that suggest that the condition may be more frequent than suspected (Lightwood, 1932; Baggenstoss and Keith, 1941; Brown and Richter,

1941; Field, 1946; Stryker, 1946, 1947; Mant et al., 1952; Traisman et al., 1956; Moran and Becker, 1959; Franciosi and Blanc, 1968; Bor, 1969; Witzleben, 1970). Most of the deaths occurred suddenly, usually between the neonatal period and two years of age. Some were associated with coronary thrombosis; others with acute onset of congestive heart failure, that was found at autopsy to have been related to coronary arteriosclerosis or to endocardial fibroelastosis (EFE) or both. James (1967) reviewed the conditions associated with hereditary medial necrosis of the small coronaries and other abnormalities (e.g., alcoholic cardiomyopathy, and diabetes mellitus), in which such lesions are found and considered the susceptibility of such patients to arrhythmias and conduction disturbances. He commented on the similarity of the lesions of the small coronaries of Mg-deficient dogs (Wener et al., 1964) and those of alcoholic cardiomyopathy (Pintar et al., 1965), which he suggested might be related to their hypomagnesemia. Thomas et al. (1956) suggested that "an unknown agent" is etiologic in both calcific arterial disease and EFE in infancy, which often coexist. Oppenheimer and Esterly (1967) correlated half of 57 instances of infantile EFE with coronary or generalized arteriosclerosis or focal myocarditis, among 148 hypertensive infants and children. One, a year-old infant with all three CV abnormalities, also had marked hyperplasia of the juxtaglomerular apparatus, such as Cantin (1970) and Cantin and Huet (1973) have shown in Mg-deficient rats. We speculate that Mg deficiency, prenatally or perinatally, may be contributory to these human disorders, as reported in about 3,000 infants from birth to 2½ years of age (Seelig, 1980).

Table 6. Infantile Arteriosclerosis
(possible relationship to prenatal and neonatal Mg deficit)

Usually involves small coronaries (as in experimental Mg deficiency)
Arteriosclerosis is sometimes generalized
Major coronary thrombosis occurs rarely
Often associated with endocardial fibrelastosis (as seen in hypervitaminosis D)
Often associated with sudden unexpected death (Mg deficiency implicated in sudden cardiac death)
Involvement of infants at high risk of Mg deficiency:
-Premature or small for gestational age infants
-Infants of pre-eclamptic or eclamptic mothers
-Infants of hyperparathyroid mothers
-Infants with birth asphyxia (leads to immediate increase of serum Mg as Mg leaves cells; followed by hypomagnesemia)
Findings suggestive of Mg deficiency in infancy:
-Transitory hypoparathyroidism
-Ca-resistant hypocalcemia
-Vitamin D refractoriness

Cardiovascular Disease of Hypervitaminosis D; Possible Role of Magnesium Loss

Vitamin D, an agent that causes hypomagnesemia when given in excess

(Richardson and Welt, 1964; Seelig, 1971), has long been known to cause arteriosclerosis, and to play a role in infantile hypercalcemia and the supravalvular aortic stenosis syndrome (Seelig, 1969). (See Table 7.) It has also been implicated in experimental (rabbit) EFE, and possibly in infantile EFE (Coleman, 1965); its incidence, and that of infantile hypercalcemia and of the C V sequellae, declined in England when excessive vitamin D intakes were reduced. The similarity of infantile coronary and generalized arteriosclerosis to the lesions of hypervitaminosis D suggested vitamin D as a possible etiologic factor to several of the investigators, who considered hyperreactivity to vitamin D among the children whose vitamin intakes did not seem excessive (Lightwood, 1932; Brown and Richter, 1941; Field, 1946; Stryker, 1947; Mant et al., 1952; Wahlgren, 1952; Moran and Becker, 1959; Rashkind et al., 1961; Meyer and Lind, 1972).

Table 7. Hypervitaminosis D (Toxic Doses or Hyperreactivity) in Animals and Man (Possibly related to induced Mg loss and excess Ca)

Hypercalcemia	Supravalvular aortic stenosis
Hypercholesterolemia	Generalized atherosclerosis with marked calcification
Hypertension	
Increased Mg loss (urinary)	Endocardial fibroelastosis

Additional support of this possibility is the hypercholesterolemia and hypertension in children and adults on toxic doses of vitamin D (Frost et al., 1947; DeLangen and Donath, 1956; Lang and Eiardt, 1957; Amann, 1959; Beuren et al., 1964, 1966), or in infants, children, and adults with hyperreactivity to vitamin D (Schlesinger et al., 1952; Lowe et al., 1954; Stapleton and Evans, 1955; Bongiovanni et al., 1957; Schwartz, 1957; Singleton, 1957; Fellers and Schwartz, 1958; Snyder, 1958; Hooft et al., 1961,1963; Linden, 1974,1977).

The degree to which vitamin D excess (i.e., in the fortified infant formulas plus vitamin supplements) may contribute to the greater involvement of the larger arteries, usually seen later in infancy and early childhood (with elastica degeneration, lipid degeneration, calcification, and to hypercholesterolemia and hypertension), requires further study. The full-term infant normally requires as little as 100 I.U. of vitamin D daily; the amount needed by most adults is considered so small as to be met by exposure to sunlight and by natural foods (Recommended Dietary Allowances, 1968). A survey showed that half of the 150 young Americans studied ingested 400-800 I.U. daily, and almost 10% consistently ingested over 1000 I.U. each day (Dale and Lowenburg, 1967).

Interrelations of protracted high intakes of vitamin D with Mg requirements, and with the CV lesions of imbalance, deserves study (Seelig, 1978). Epidemiologic data, correlating moderately high vitamin D intakes with increased incidence of MI (Linden, 1974,1977), suggest that in northern Norway, where intakes of natural vitamin D-rich foods is customary, the incidence of hypercholesterolemia and susceptibility to sudden death from IHD seems to be related to the amount of vitamin D ingested and to the individual sensitivity to solar irradiation. Even slightly to moderately increased vitamin D intakes for relatively short periods have increased serum cholesterol levels in normal adults (Feenstra and Wilkens, 1965; Fleischman et al., 1970). Worthy of note, is the increased serum cholesterol of experimental vitamin D toxicity (McAllister and Waters, 1950; DeLangen and Donath, 1956; Hass

et al., 1961). There are few data on the Mg status of patients with hypervitaminosis D. Although, rarely, low serum Mg levels have been reported in patients overdosed with vitamin D (Frost et al., 1947) or in the early stage of infantile hypercalcemia (Lowe et al., 1954), and increased levels of Mg developed on discontinuing the vitamin D, in other instances the serum Mg levels were normal (Lowe et al., 1954; MacDonald and Stapleton, 1955; Fellers and Schwartz, 1958; Forfar, 1958). The renal damage, caused by vitamin D toxicity, and the customary use of milk of magnesia to manage the constipation that is characteristic of vitamin D toxicity, makes the isolated reports of serum Mg levels difficult to evaluate. Furthermore, tissue levels of Mg may be low in patients with chronic renal disease, despite normal or high serum levels (Massry and Coburn, 1970; Lim and Jacob, 1972). Dalderup (1960) was the first to speculate that the damage of infantile hypercalcemia might be related to cellular Mg deficiency, a hypothesis that seems reasonable in light of the further data now available.

Possible Genetic Factors in Infantile Arteriosclerosis; Consideration of Pediatric Genesis of Cardiovascular Disease Later in Life

The identification of infantile coronary arteriosclerosis, or of sudden death with convulsions or of unknown origin (no autopsy having been done) in siblings of infants whose coronary disease was identified at autopsy, has suggested a genetic abnormality leading to premature arterial elastica degeneration and calcification (Menten and Fetterman, 1948; Traisman et al., 1956; Hunt and Leys, 1957; Moran and Becker, 1959; Chipman, 1960; Meurman et al., 1965; Witzleben, 1970). Since Mg deficiency and vitamin D excess have each been implicated in such changes, and since genetic abnormalities in intestinal absorption and in renal tubular reabsorption of Mg have been identified (infra vide), as has hyperreactivity to vitamin D (Seelig, 1969), the possibility that these genetic factors may contribute to CV damage in infancy, and perhaps later in life, should be considered.

Systematic postmortem study of the vasculature of stillborn infants, as well as of infants dying with convulsive or hyperirritable disorders, including victims of the sudden infant death syndrome (in whom the possibility of Mg deficiency is under investigation (Caddell, 1972,1977; Durlach et al., this symposium) should be undertaken. Until examination of the arteries of infants, dying of all causes, becomes routine, and until the small coronaries are carefully examined (even when there seems little reason to supect cardiac disease), the actual incidence of infantile arterial disease will remain uncertain. Measurement of myocardial Mg may be rewarding, if the observations of Lehr (1965a,b, 1969) in small animals are applicable to infants, as they seem to be in adults (Seelig, 1972b).

The revived interest in the possibility that adult CV disease has its roots in infancy, and that the initial abnormality may be in the musculoelastic layer of the arteries of infants and children (Danilevicus, 1974; Neufeld, 1974), recalls the earlier consideration of atherosclerosis as a pediatric disease, the earliest manifestations of which were described as intimal, with fatty streaks (Duff and McMillan, 1951; Holman, 1961; Strong and McGill, 1969). That the two theories are not mutually exclusive is indicated by the lipid droplets seen in conjunction with damaged elastica (Duff and McMillan, 1951), and by the evidence that elastica degeneration predisposes to lipid deposition (Kramsch et al., 1971). Dock (1946), Fangman and Hellwig (1947), and Wilens

(1951) commented on the diffuse intimal thickening that occurs early in life as an early change leading to atherosclerosis. Schornagel (1956) considered the intimal thickening, particularly of the coronary arteries, reflective of the high demands on the coronaries in the first few months of life that provide a basis for coronary sclerosis later in life. Focal lesions of the internal elastic lamina have been reported in the very young; rupture and degeneration of the internal elastic membrane are the earliest lesion, followed by fibrous proliferation and intimal thickening; rapid progression ensues in the early months (Levene, 1956; Moon, 1957; Zugibe and Brown, 1960; Bertelson, 1961; Kaunitz, 1961).

Retrospective studies of adults with early CV disease for histories of prenatal or infant abnormality may prove interesting. Of greater value would be long-term follow-up of infants born to mothers with preeclampsia, eclampsia, or diabetes (who have been shown to have low Mg levels, infra vide), or who survived birth asphyxia or convulsive episodes. Comparison of blood Mg, Ca, PO_4, and lipids, and of the blood pressures of infants on different feedings, may help to clarify some of the etiologic factors in infantile and later arteriosclerosis.

Prenatal Arterial Damage, Possibly Related to Maternal Magnesium Deficiency

Prenatal coronary arterial injury has been considered, particularly among premature infants and among those born to toxemic mothers or to mothers with hyperparathyroidism of pregnancy (Baggenstoss and Keith, 1941; Stryker, 1946; Bacon, 1964). Surveys of the coronary arteries of stillborn and newborn infants have shown arterial damage in a surprisingly high percentage. Dock (1946) and Fangman and Hellwig (1947) found that a third of such autopsied infants had thickening of the coronary arterial intima. The latter considered the frayed elastica, in association with lipid droplets, indicative of an early stage of arteriosclerosis.

The fact that such lesions are seen in Mg deficiency suggests that the long-known decrease in Mg levels in eclampsia (Hirschfelder, 1934; Wolff et al., 1937; Haury and Cantarow, 1942; Hall, 1957; Achari et al., 1961), and even in less seriously abnormal or in normal pregnancy (Hurley, 1971) may be contributory to prenatal and neonatal arterial disease. The retention of high percentages of pharmacological doses of Mg (given to control the signs of toxemia of pregnancy, some of which resemble those of Mg deficiency) has been considered suggestive of underlying Mg deficiency (Hall, 1957; Flowers, 1965; Dumont and Bernard, 1966; Hurley, 1971; Kontopoulos et al, this symposium). Women with habitual miscarriage, threatened abortion, or premature labor have been found to have much lower serum Mg levels than do women with normal pregnancies (Ryvkis, 1967 these findings may be relevant to the high fetal losses in Mg-deficient pregnant rats (Dancis et al, 1971; Hurley, 1971; Wang et al, 1971; Hurley et al,1974). The reports list no surviving young born to severely deficient rats, when the deficiency was maintained throughout pregnancy. Shorter periods of deficiency, during the first half of pregnancy, resulted in resorption of the implantation sites or fetal malformation or death in high percentages (Hurley, 1971).

The better fetal salvage rate among Mg-treated toxemic mothers, as compared with that of comparable mothers treated with tranquilizers, antihypertensives, and anticonvulsants (Zuspan and Ward, 1965; Holman and Lipsitz, 1966) supports the premise that Mg inadequacy during preg-

nancy can contribute to infant disorders, possibly including damage to the CV system.

Birth asphyxia has been blamed for the coronary arterial necrosis seen in almost 10% of stillborn infants and among those dying within three days of birth (Gruenwald, 1949). Loss of tissue Mg may also be of importance in this group, since cellular Mg is lost in response to asphyxia, with immediate hypermagnesemia, followed by hypomagnesemia (Engel and Elin, 1970; Tsang et al., 1974).

Factors in Hypomagnesemia of Infancy

There are many reports of hypomagnesemia in infancy (Ferlazzo, 1971; Henrotte and Durlach, 1971; Tsang, 1972). Ferlazzo (1971) has reviewed the evidence that there is a strong correlation between maternal and fetal Mg blood levels. Infants born to toxemic mothers, or who are small for gestational age, or who are premature, have subnormal serum Mg levels (Tsang and Oh, 1970; Tsang et al., 1973; Zigliera et al., 1973; Tsang and Brown, 1977; Tsang et al., this symposium), as do those born to diabetic mothers (Tsang et al., 1977, this symposium). Maternal hyperparathyroidism, with secondary transitory infantile hypoparathyroidism (Davis et al., 1965) can contribute to both infantile hypocalcemia and hypomagnesemia. Additionally, hypomagnesemia has been shown to interfere with PTH release (Anast et al., 1972; Anast, 1977), and to the calcemic response to PTH and to vitamin D (Atwell, 1966; Salet et al., 1966; Anast, 1967; Estep et al., 1969; Connor et al., 1972 Woodard et al., 1972; Rosler and Rabinowitz, 1973). Hypomagnesemic hypocalcemia has been recorded as responsible for 20-34% of neonatal convulsions, to which 1-2% of infants up to 28 days of life are subject (Forfar et al., 1973; Cockburn et al., 1973).

Even healthy infants have been found to have significantly low serum Mg levels up to the third month of life (Kobayashi, 1967). The levels of breast-fed infants have been reported higher than of cow's milk-formula-fed infants (Anast, 1964; Gittleman et al., 1964; Harvey et al., 1970; Forfar et al., 1973), possibly an effect of the disproportionately high PO_4 content of cow's milk, as compared with mother's milk (Gittleman and Pincus, 1951; Anast, 1964; Coussons, 1969; Snodgrass et al., 1973, Cockburn et al, 1973; Seelig, 1978, 1979).

It is conceivable that such infants may be the human counterpart of Lehr's experimental model: PT PO_4-loaded rats, that develop abnormalities of the coronary microcirculation (Lehr, 1959, 1965b; Lehr et al., 1967). The underlying Mg deficit may increase the potential CVP effect of the PTH deficiency, which may be intensified by the high PO_4 content of cow's milk. The fortification of cow's milk with vitamin D may also be contributory.

Malabsorption of Mg has been identified in infancy and has been considered a genetic abnormality (Paunier et al., 1965; Salet et al., 1966; Friedman et al., 1967; Skyberg et al., 1967; Paunier et al., 1968; Skyberg et al., 1968; Stromme et al., 1969; Haijamae and MacDowall, 1972; Unsigned Editorial, 1973). Defective renal tubular reabsorption of Mg in the ascending limb of the loop of Henle (Dirks, 1976) may be another genetic abnormality that contributes to the syndrome in infants, that is associated with hypochloremia, hypomagnesemia, and normotensive aldosteronism (Sutherland et al., 1970; Mace et al., 1973; Kurtzman and Gutierrez, 1975; Seelig et al., this symposium). Other factors contributing to pediatric hypomagnesemia have been reviewed by Paupe (1971); they include enteric losses, i.e., as a result of severe diarrhea (Sa-

vage and McAdam, 1967; Harris and Wilkinson, 1971) and in hepatobiliary disease in infancy (Kobayashi et al., 1974). Such infants may exhibit tremulousness, shivering, and other signs of neuromuscular irritability (Wong and Teh, 1968; Chhaparwal et al., 1973).

Soft/Hard Water, Magnesium, and Sudden Death from Ischemic Heart Disease

Comparison of the infantile vasculature and myocardial Mg levels in stillborn and neonatal fatalities in soft and hard water areas may also be rewarding, higher infant mortality rates having been reported in soft than in hard water areas (Crawford et al., 1972). In this regard, it may be germane that the improved fetal salvage rates, that were seen in treatment of maternal toxemia with Mg, were reported from geographic areas with soft water (Seelig and Bunce, 1972).

There has been controversy as to whether it is Ca or Mg in hard water that is the protective factor against sudden death from IHD, or whether there is something in soft water that is toxic (Seelig and Bunce, 1972; Seelig and Heggtveit, 1974; Harman, 1977; Seelig, 1977). Much of the experimental evidence that shows that increased Ca increases vascular lesions, whereas Mg is protective, is presented here. Part II considers the contrasting effects of Mg and Ca on arterial resistance and blood flow. Data, referable to the contrasting effects of Mg and Ca on myocardial metabolism and irritability have been evaluated elsewhere, particularly in reference to the protective effects of Mg, but not Ca, against arrhythmia (Seelig, 1972b; Seelig and Heggtveit, 1974). **Evidence** that the incidence of cardiac lesions is higher and the cardiac and arterial Mg levels are lower in those who had lived in soft rather than in hard water areas (Crawford and Crawford, 1967; Anderson et al., 1973; Chipperfield and Chipperfield, 1973; Anderson et al., 1975), whereas the levels of other cations do not differ significantly (Anderson et al., 1975; this symposium) further supports the contention that it is the Mg in the hard water that is protective. The marginal Mg intake of the Occidental diet (Seelig, 1964; Schroeder et al., 1969), that has been falling in the United States since the turn of the century (Friend, 1967), is probably insufficient to protect against the high intakes of such nutrients as PO_4 (a major source of which is soda, such as the colas (Lutwak, 1974), highly salted fatty and high carbohydrate snack foods, high fat, protein, and vitamin D intakes. It is disconcerting to realize that the CVP diet, developed by Sos et al. (1960) resembles the American diet in so many ways. In the United States, where vitamin D fortification of milk has been mandatory in most states since the middle 1930s and where other sources are popular, intakes considerably above the antirachitic requirements are almost unavoidable.

It seems plausible that the increasing incidence of IHD from 1901-1961 (Anderson and LeRiche, 1970) and the evidence that among men 20-34 years of age with cardiac abnormalities (who died in aircraft accidents) the incidence of coronary artery disease has risen to 86% of those with diagnosed CV disease (Pettyjohn and McMeekin, 1975). Analysis of the age distribution indicates increasing incidence in the young age groups. This may reflect the multifactorial pattern of nutritional imbalances: increasing PO_4, salt, and vitamin D, as well as of sugar, and protein, in the face of declining Mg intakes. In such a situation, the amount of Mg supplied by hard water (Hankin et al., 1970) may be critical (Anderson et al., 1975; this symposium).

MAGNESIUM DEFICIENCY: LOSS OF POTASSIUM, RETENTION OF CALCIUM AND SODIUM

Magnesium deficiency causes both tissue and serum losses of Mg; without Mg repletion, the K deficit persists (Whang et al, 1967). (See Table 8.) Conversely, the Mg-deficient animal retains Na, although this is usually manifest in tissues, rather than in serum. The animals generally exhibit peripheral, hepatic, and myocardial edema (Cantin, 1970; Elin et al., 1971). A comparable clinical picture has been reported in infantile hypomagnesemic hypocalcemia with hyponatremia and edema (Chiswick, 1971), and in a woman with renal Mg wasting and normocalcemic latent tetany of marginal Mg deficiency (Seelig et al., 1975; this Symposium), who exhibited Na retention, but normotensive or hypotensive intermittent aldosteronism, only on challenges that increased her Mg loss (Seelig et al, this Symposium). Her clinical picture, and that of the infants described by Chiswick (1971), somewhat resemble that of the patients with the normotensive aldosteronism of Bartter's syndrome, who also have hypomagnesemia (Sutherland et al.,1970; Mace et al.,1973). In this form of Mg deficiency, as in the "pure" Mg deficiency animal models, hypertension is not part of the syndrome, and serum Ca tends to remain normal or fall.

Table 8. Electrolyte Changes of Magnesium Deficiency

	Serum				Soft Tissue				
	Mg	K	Na	Ca	Mg	K	Ca	Na	H_2O
In Experimental Models									
Balanced Diet -except for < Mg	↓	↓	±	↓	↓	↓	↑	↑	↑
Calcemic Diet -> Ca, PO_4 ± vitamin D > vitamin D	↓	↓	↑	↑	↓	↓	↑	↑	↑
Hormonal Imbalance									
↑ PTH -2° to < Mg, Ca									
- idiopathic - exogenous	↓	↓	↓	↑	↓	↓	↑	?	?
↑ Corticoid (MCS)	↓	↓	↑	↑	↓	↓	↑	↑	↑
↑ Catecholamines	±	±	±	±	↓	↓	↑	↑	?
ESCN[a]	±	±	±	±	↓	↓	↑	↑	?
PT_x + Na + PO_4	±	±	±	±	↓	↓	↑	↑	?
Myocardial Anoxia									
-Early	↑	↑	±	±	↓	↓	↑	↑	↑
-Late	↓	↓			↓	↓	↑	↑	↑
In Man									
Severe Mg Deficiency									
Neonatal, Malabsorption, Renal Wasting	↓	↓	±	±	↓	↓	↑	↑	↑
Diuretics	↓	↓	±	±↑	↓	↓	↑	↑	↑
Marginal Mg Deficiency	?	?	?	?	?	?	?	?	?
(with calcemic, > fat, >salt, > sugar)	±↓			↑			↑		

a: Electrolyte Steroid Cardiac Necrosis (MCS +Na + PO_4)
> = excess; ↑ = increased; ↓= decreased

The emphasis, in this presentation, has been on the hypocalcemia of severe Mg deficiency, such as is seen in the neonate (and is postulated to play a role in the roots of arteriosclerosis) and in older patients, and that is associated with hypoparathyroidism and decreased response to vitamin D. The marginal Mg deficiency, (more common in older infants, children, and adults with parathyroids that respond to low Mg by hypersecretion and possibly hyperplasia, as in calves (Larvor, 1971) is likely to result in a high Ca/Mg ratio, whether in the tissues or the blood. Interrelationships of Mg, Ca, vitamin D, and PT function were reviewed at the First International Symposium on Magnesium, in Vittel (Larvor, 1971; Seelig, 1971), as providing some insight into differences in calcemic responses to Mg deficiency. Massry and Coburn (1973), Nielsen (1974), and Anast (1977) have most recently reviewed and integrated the newer data, and there have been important new contributions presented at this Symposium.

The infarctoid experimental model (Sos et al., 1960), in which Mg (and K) deficiency is complicated by agents that increase the serum Ca as well as cholesterol, is characterized by hypertension. It, like the other Mg deficiency models, is also characterized by Na retention and K loss, as well as elevated Ca-in the tissues, if not always in the serum. The resultant combined electrolyte abnormalities (high Ca and Na; low Mg and K) set the stage for Haddy's physiologic studies (Part II) that show what such abnormalities do to the resistance of the arteries to blood flow.

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