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Magnesium deficiency with phosphate and vitamin D excesses: Role in pediatric cardiovascular disease?

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Evidence of pediatric arteriosclerosis as the initiating lesion leading to premature death from ischemic heart disease has led to assessment of various dietary and genetic factors as etiologic agents in the pathogenesis of pediatric hyperlipidemia and atheromata. The similarity, for example, of the cardiovascular lesions caused by experimental "pure" magnesium deficiency to those seen in certain infants born dead, or dying in the neonatal period, suggests that prenatal magnesium deficiency might play a contributory role in these deaths. Emphasis has thus been placed on assessing the customary low magnesium intakes of pregnant women and their tendency toward hypomagnesemia during the first and third trimesters, as well as on the placental insufficiency associated with eclampsia, a condition in which magnesium deficiency is likely. The correlation of congenital cardiovascular and other defects with placental lesions, both of which have been produced by vitamin D excess (which intensifies magnesium deficiency), suggests that a low magnesium to vitamin D ratio might be pathogenic in intrauterine malnutrition, infantile arteriosclerosis, stenotic valvular disease, and endocardial fibroelastosis. The intensification of experimental cardiovascular lesions by parathyroidectomy and by phosphate excess and calcemic agents such as vitamin D (which is also hyperlipemic) suggests that neonatal hypoparathyroidism, hyperphosphatemia, and hypomagnesemic hypocalcemia (seen almost exclusively in cow's-milk-formula-fed infants) might be factors that establish pediatric arteriosclerosis. Infants with metabolic abnormalities that increase the need for magnesium, such as magnesium malabsorption, or those born to mothers with diabetes mellitus, are more vulnerable to sequelae of dietary magnesium deficiency that is intensified by high intakes of nutrients that reduce magnesium absorption or increase its renal excretion. Identifying these infants is of prime importance.

The factors responsible for the rise in incidence of morbidity and mortality from cardiovascular disease seen during this century remain uncertain. Still to be proved is whether dietary habits have played a causative role or whether they can reduce the risk of the sudden death from ischemic heart disease (IHD) that has emerged as a major problem, especially in men under 50.[1-5] Because lowering elevated blood cholesterol in cardiovascular patients has not reduced the incidence of IHD,[5-8] it has been suggested that the saturated fat intake should be lowered in infancy and that major dietary alterations be followed throughout life.[9] The emphasis of extensive research programs has been almost exclusively on lowering blood lipid levels. The suggestion that infant diets be changed derives largely from the fatty intimal streaks that have been found in the arteries of infants and young children[10-13] and from the observation that the children of young IHD victims show a high incidence of hyperlipidemia.[14-16] However, the theory that excessive dietary fat is the major etiologic factor in atherosclerosis has been criticized and the need for reappraisal of the evidence has been emphasized.[17] Fibromusculoelastic arterial changes in infants and children have long been recognized in pediatric arteriosclerosis[18-21] and have recently been implicated as early lesions in atherosclerotic disease.[22,23] Fibroblastic proliferation of the intima and calcification of damaged elastica fibers and musculoelastic degeneration of coronary arteries, demonstrated in the neonatal period, have been shown to become more severe in the postnatal months.[18-23] That the two theories (arterial fatty infiltration and fibromusculoelastic damage) are not mutually exclusive is suggested by the lipid

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droplets seen in conjunction with damaged elastica.[18,24,25] Thus, we should consider the possibility that nutritional imbalances that cause damage to the arterial elastica and muscularis in experimental models might participate similarly in clinical disease.

Perinatal magnesium deficiency and imbalances that increase magnesium requirements, directly or indirectly, may be contributory factors in the twentieth century epidemic of premature cardiovascular disease. Experimental "pure" magnesium deficiency causes lesions in the small coronary arteries and perivascular myocardium similar to those seen in infantile arteriosclerosis.[26] Damage to the larger coronary and peripheral arteries is noted in animals that are also given dietary excesses of calcium, phosphate, and vitamin D, all of which increase magnesium requirements.[26,27] Similarly, experimental cardiac damage is associated with magnesium deficiency, intensified by factors that increase magnesium loss, and protected against by magnesium administration.[26,28-31] Thus, perinatal magnesium deficiency may be a predisposing factor in pediatric arteriosclerosis, which is intensified early in life by feeding vitamin D–fortified cow's milk formulas and by providing additional vitamin D supplements, a risk that is increased by hyperreactivity to vitamin D.[32] Vitamin D has also been shown to cause hyperlipidemia and has been implicated in IHD, even in doses that are only moderately above those commonly recommended.[33] The dietary changes in the affluent countries during this century include a decline in magnesium intake[34] to a degree at which negative magnesium balance is common in young adults on self-selected diets, particularly in men[35] and during pregnancy.[36] The shift from breast feeding to cow's milk formulas has resulted in hyperphosphatemia of infancy with associated hypocalcemia and hypomagnesemia. The ingestion of phosphate-rich foods and beverages and the widespread use of therapeutic antirachitic doses of vitamin D, i.e., doses high enough to cure rickets, both in multivitamin supplements and in milk and other foods, not only during infancy but during childhood, adolescence, and adult life, may increase magnesium requirements and intensify cardiovascular lesions.[26-32]

Table 1. Cardiovasopathic diet and pathologic and biochemical changes it induces in rats

Composition of CVP diet

Low content	Normal content	High content
chloride	calcium	cholesterol
magnesium		fat, saturated
potassium		phosphate
		protein
		sodium
		vitamin D_2, D_3

Changes induced by CVP diet

	Serum (mEq/l)				Myocardium (mEq/kg)			
	Ca	K	Mg	Na	Ca	K	Mg	Na
Control diet	4.8	8.1	2.5	133	4.7	63	14.5	52
CVP diet	5.0	6.6	2.0	134	5.5	42	11.7	61

	Serum cholesterol	Blood pressure (mm Hg)	Incidence of MI
Control diet	94 mg%	112 mm Hg	0
CVP diet	↑ 5- to 6-fold	↑ ca. 50 mm Hg	80-90%
without cholesterol	↓ to < 50% CVP level	= CVP BP	↓ to 60%
without vitamin D	= CVP level	↓ 30 mm below CVP BP	↓ to 40%
with normal protein	↑ to 15% > CVP	= CVP BP	↓ to 40%
with normal salts	↓ to < 50% CVP level	± ↑ CVP BP	↓ to 13%

Experimentally induced cardiovascular damage

Cardiovascular lesions arising in animals kept on a magnesium-poor but otherwise fairly well balanced diet are found predominantly in and around the small coronary arteries. In rats[37-39] and dogs,[40-42] lesions include

Table 2. Major differences in electrolyte contents between a normal diet and the CVP diet

Salts	Normal diet*	CVP diet*
K_2HPO_4	342	0
$NaHPO_4 \cdot 12H_2O$	0	170
$NaH_2PO_4 \cdot 2H_2O$	0	170
NaCl	168	270
$NaClO_4 \cdot H_2O$	0	80
$MgSO_4 \cdot 7H_2O$	170	0

*g/kg (dry weight);
CVP = *cardiovasopathic*

intimal edema and proliferation, degeneration, and fragmentation of the elastica, and perivascular focal myocardial infiltration, edema, and necrosis. Similar lesions in magnesium-deficient cows are provocative, since they occur spontaneously late in pregnancy and during early lactation in herds pastured in areas with magnesium-poor soil.[43,44] Calcification of the larger coronary arteries, aorta, and peripheral arteries develops when the magnesium-low diet is high in calcium or vitamin D.[27,28,40,44-50] These lesions, which include endocardial thickening, are usually found in association with intimal plaques and fragmented elastica.[26] Studies of interrelationships of magnesium deficiency and excess dietary fat in the pathogenesis of atherosclerosis have shown dissociation between serum and arterial lipids in response to modification of the magnesium and calcium intakes.[51,52] Magnesium supplementation in animals on atherogenic regimens exerted little influence on total hyperlipemia and sometimes raised the blood cholesterol level. Serum lipoproteins and arterial lipid deposition, however, fell. High dietary calcium to magnesium ratios in animals on atherogenic regimens lowered the serum lipids slightly but increased lipid deposition in the arteries.[51,52] Magnesium supplementation in rats maintained on atherogenic diets for one year was associated with a gradual decline in serum lipids but a prompter and more significant decrease in arterial fat deposits.[53] Dogs on intakes of saturated fats sufficient to induce gross intimal plaques showed increased serum cholesterol levels; when their diets were supplemented with magnesium, protection against plaque formation was conferred.[50]

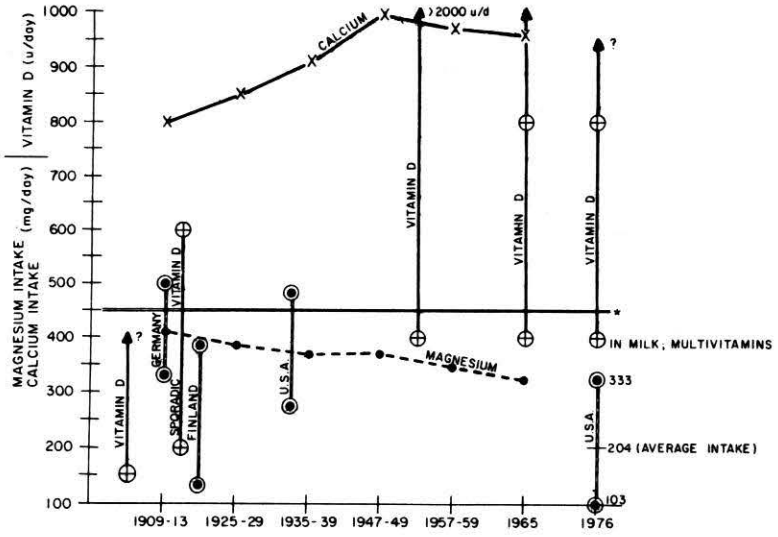
Phosphate loads have long been known to intensify the lesions of experimental models of myocardial necrosis, and magnesium and potassium chloride have been protective.[54] A cardiovasopathic (CVP) diet has been produced by combining these imbalances and providing, additionally, excess protein and fat (Table 1).[27,28,30] Although serum electrolytes showed relatively minor changes, there were sharp drops in myocardial magnesium and potassium levels and moderately increased myocardial sodium and calcium levels (Table 1). Correcting individual abnormal components of the CVP diet produced partial improvement in serum cholesterol levels and, usually, in hypertension. Providing a normal salt mixture (cited in Table 2) protected against spontaneous myocardial infarcts (Table 1), but the most protection was produced by adding fivefold higher than customary magnesium intakes to the CVP diet.

Parathyroidectomy, which increases phosphate retention, further intensifies cardiovascular lesions in phosphate-loaded animals,[26,55] an effect that has been correlated with depletion of myocardial magnesium in this and other models of myocardial necrosis.[29,55,56] In addition, ionic dysequilibria, such as are produced by the dietary imbalances described (hypomagnesemia and hypokalemia, plus hypercalcemia and hypernatremia),[26] increased the arterial resistance.[57]

Perinatal nutritional imbalances and infantile CV disease

Inadequate magnesium intake is common during pregnancy; the intake of the pregnant woman rarely

Fig. 1. Intake patterns of magnesium and other nutrients during this century



calculated average Ca intake, adult

average Mg intake

range of vitamin D intake

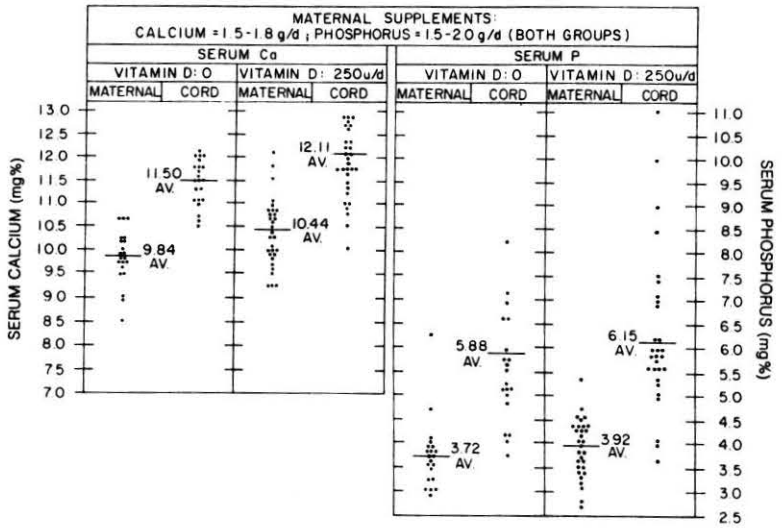
Mg intakes, pregnant women

Calcium intake has been maintained, vitamin D intake has sharply risen, but magnesium intake has steadily declined.

**recommended Mg requirement during pregnancy; Food and Nutrition Council, National Academy of Sciences, 1968*

reaches the amount (450 mg/day) recommended for pregnant and lactating women (Fig. 1).[32,34,36,58] In metabolic balance studies carried out in both European and American pregnant women during the first third of this century, it was found that maintenance of positive magnesium balance (such as is necessary for formation of new tissue) is unreliable at daily intakes under 450 mg of magnesium.[36] Many of the women ingested much less on their self-selected diets and were frequently in negative balance. The most recent such study,[58] reported in 1976, showed that diets customarily consumed by midwestern pregnant women provided between 103 and 333 mg of magnesium daily (average = 204±54 SD), amounts shown earlier to be grossly inadequate by metabolic balance studies. That such low intakes of magnesium can have adverse effects on the infants is suggested by the evidence that fetuses of rats maintained on suboptimal magnesium intakes are more magnesium-deficient than are the mothers at term and are more seriously damaged.[59-61] Pregnant rats given 10% the control amount of magnesium gave birth to pups that were smaller than normal and that had poor viability; only 7.5% of 246 survived.[61] In contrast, the deficient mothers were normal in weight and appeared otherwise normal, although they had subnormal serum and bone magnesium levels. Pregnant rats with 10-fold greater magnesium deficiency during the second half of gestation delivered small, weak, anemic, edematous pups with markedly low tissue magnesium levels.[59,60] The mothers looked healthy at term and, although hypomagnesemic, had only slightly reduced tissue magnesium levels. Greater and more prolonged magnesium deficiency during pregnancy resulted in resorption of most implantation sites or stillbirth of malformed young.[59,60,62] Why the fetus is more susceptible to the effects of magnesium depletion than is the mother requires further study. Complicated interrelationships between maternal and fetal parathyroid and calcitonin responses to hypomagnesemia that might be contributory are considered in detail elsewhere.[63] Magnesium serum levels during the first and third trimesters of normal pregnancy are below nonpregnant levels, even when corrected for hemodilution.[62-64] The extent to which magnesium inadequacy during pregnancy might cause prenatal damage, including such cardiovascular lesions as have been seen in stillborn infants and in those dying in the early neonatal period,[18-23,26] requires investigation. Testing pregnant women or postpartum women who have borne defective or stillborn infants for occult magnesium deficiency (e.g., by determining the percentage retention of a parenteral loading dose of magnesium[63,65,66]) might yield data that would justify prenatal supplementation with magnesium, as well as with calcium and vitamin D. Until it was found that leg cramps of pregnancy increased and calcium levels dropped when calcium supplements were given as the phosphate,[67] such supplements were often given to correct falling levels of calcium and phosphorus during pregnancy. In an early clinical study of the effect on fetal bone of moderately high dosage calcium and phosphorus supplements, with and without vitamin D_2 (in viosterol), it was found that maternal serum calcium and phosphorus levels rose more when the vitamin was administered; in cord blood, these values sometimes rose to pathologically high levels (Fig. 2).[68,69] These investigators were concerned about fetal osteosclerosis that might result in difficult deliveries; the latter[69] also ob-

Fig. 2. Serum calcium and phosphorus levels in maternal blood at delivery and in cord blood*



Values following maternal supplementation with calcium and phosphorus rose more sharply with vitamin D supplementation; cord blood values sometimes reached pathologic levels. Horizontal line in each scattergram represents average value.

served severe placental scarring and calcification in the group of mothers given calcium (as lactate) and vitamin D supplements, as well as renal calcification in several stillborn infants from that group. Cardiovascular tissues were not examined.

Experimental magnesium deficiency has also caused increased placental calcification.[59] Since vitamin D excess causes both magnesium loss and placental abnormalities[70,71] not unlike changes seen in human eclampsia,[72] a condition that is commonly treated with pharmacologic doses of magnesium, the possibility that prenatal magnesium deficiency may play an etiologic role in some complications of pregnancy is worth considering. Only rarely has the retention of high percentages of the high doses of magnesium given to preeclamptic and eclamptic women been interpreted as suggestive of maternal magnesium deficiency[36,62,63,66] and, by inference, of fetal deficiency. A high percentage of congenital abnormalities, which are common in infants with intrauterine growth retardation (often secondary to placental insufficiency), are cardiovascular.[73] Furthermore, both magnesium deficiency[26] and vitamin D excess[32] have been implicated in severe cardiovascular damage including arterial, valvular, and endocardial lesions (Table 3).[26,63]

Hypomagnesemia is rarely diagnosed in infancy unless concomitant hypocalcemia and convulsions are not responsive to treatment with calcium infusion or calcemic agents. Infants at greatest risk of neonatal hypomagnesemia are low-birth-weight infants (such as are often born to toxemic mothers, having a high likelihood of placental insufficiency), those born to very young primiparous women or to young mothers who had had frequent pregnancies or multiple births (and are thus more subject to magnesium deficiency), and to diabetic mothers.[63,74-78] Plasma magnesium levels are a less reliable index of magnesium deficiency than is the parenteral loading test.[63,65,79,80] Neonatal magnesium deficiency so demonstrated has been shown to be more common in premature infants than in term infants, even when serum magnesium levels are within normal limits.[81]

Neonatal hypoparathyroidism, or end-organ unresponsiveness to parathyroid hormone,[82,83] long speculated to be the cause of neonatal hyperphosphatemia, has been clearly demonstrated.[84] Very low levels of immunoreactive parathyroid hormone levels have been found in cord blood in association with high cord blood levels of calcium during the first two days after birth, in association with low serum calcium but not necessarily with high phosphorus.[84] It seems plausible that perinatal magnesium deficiency

Table 3. Similarities of infantile cardiovascular disease to lesions of experimental magnesium deficiency and of hypervitaminosis D

Clinical infantile cardiovascular disease	Experimental magnesium deficiency	Experimental vitamin D toxicity
Arteriosclerosis of the small coronary arteries intimal edema, thickening elastica degeneration: fat streaks, calcification medial edema: necrosis medial hyperplasia	Arteriosclerosis of the small coronary arteries intimal edema, thickening elastica degeneration: lipid droplets, calcification (±) medial edema: necrosis medial hyperplasia	Atherosclerosis and arteriosclerosis of the larger coronary arteries and aorta intimal plaques elastica degeneration, calcification
Endocardial fibroelastosis	Endocardial fibrosis (rare)	Endocardial fibroelastic thickening*
Valvular malformations (usually stenotic)		Supravalvular aortic stenosis*
Coronary thrombosis (rare)	Myocardial perivascular focal infiltration, edema, necrosis	Myocardial focal necrosis
Conduction abnormalities†	Electrocardiographic abnormalities	
Hyperlipidemia‡	Hyperlipidemia	Hyperlipidemia
Hypercalcemia‡		Hypercalcemia
Hypertension‡		Hypertension
Generalized arteriosclerosis‡		
Supravalvular aortic stenosis‡		Magnesium loss, intensification of magnesium deficiency

**young of rabbits with vitamin D toxicity during pregnancy; †possibly contributory to sudden infant death; ‡in later infancy, childhood*

might be involved in the pathogenesis of neonatal hypocalcemia through interference with parathyroid activity, by affecting either secretion or release of the hormone[63,85] or mobilization of bone minerals.[63,86]

The shift from breast milk to cow's milk formulas may also have contributed to the increased incidence of early cardiovascular disease documented in this century. The predominant problem is the high ratio of phosphorus to both calcium and magnesium in cow's milk. This excessive phosphorus contributes to infantile hyperphosphatemia, an effect little influenced by vitamin D.[87] The mean serum calcium levels in cow's-milk-fed infants differed little from those in breast-fed infants. However, the range was wide in the formula-fed infants, and about 15% of those supplemented with vitamin D developed serum calcium levels below 8 mg% on day 5.[86] Plasma or serum magnesium levels tend to rise during the neonatal period in breast-fed infants and to fall in those on formula.[75,88-91] The differences between magnesium and calcium levels in breast-fed and bottle-fed infants have been reduced by modifying the formulas to resemble mother's milk;[84,91] formula-fed infants' phosphate levels have also been lowered, but not to the levels of breast-fed infants.[92]

Hypomagnesemia has been recognized most frequently upon failure of infants with hypocalcemic tetany or convulsions to respond to therapeutic measures designed specifically to raise serum calcium levels. A recent controlled study[93] has shown that significantly better control of irritability was achieved by magnesium therapy than by calcium or phenobarbital, in terms of both the number of doses required to control the seizures and the plasma calcium and magnesium levels (Table 4). Whether such evidence of magnesium deficiency in infancy supports the premise that such infants are also at risk of cardiovascular lesions remains to be proved.

Nutritional imbalances and cardiovascular lesions

It is disheartening to compare the dietary imbalances that have proved effective in developing experimental models of cardiovascular disease with the imbalances detected during the perinatal and later periods of life. The typical American diet, which is marginal or low in magnesium,[35] is usually rich not only in saturated fats, proteins, and salt but often also in phosphate and vitamin D,[26,63] a diet that almost duplicates the CVP diet (Table 1).

Magnesium deficiency has clearly been shown to cause coronary and cardiac lesions similar to those found in as many as one-third of all infants born dead or who die within a few days of birth[18,26,63] (Table 3). The observation that parathyroidectomized phosphate-loaded rats develop disease of the coronary microcirculation[55,56] suggests that prenatal magnesium deficiency and neonatal hypoparathyroidism and hyperphosphatemia might contribute to the comparable clinical disease. The similarity of lesions seen in patients with hereditary medial necrosis of the small arteries to those seen in magnesium deficiency in dogs[41] has been noted, as has the possibility that magnesium deficiency–induced damage to the conduction system may play a role in the pathogenesis of arrhythmias and conduction abnormalities.[63,94] It is possible that magnesium deficiency might participate in the sudden infant death syndrome, since infants with premonitory signs

Table 4. Neonatal tetany: clinical responses to various agents

	Magnesium therapy (37)		Calcium therapy (34)		Phenobarbital therapy (33)	
Parameters	**pretreatment**	**posttreatment**	**pretreatment**	**posttreatment**	**pretreatment**	**posttreatment**
plasma magnesium (mEq/l)	1.18±0.34	1.75±0.41	1.21±0.18	1.27±0.22	1.17±0.22	1.28±0.21
plasma calcium (mg%)	6.16±0.64	8.19±0.97	5.80±0.72	7.24±1.12	6.11±0.66	7.05±1.06
inorganic serum phosphate (mg%)	9.7±1.05	9.02±1.42	9.94±1.04	8.94±1.26	9.71±1.32	8.53±1.13
number of seizures before cure	1.86±0.9	3.24±4.23*	1.72±0.9	8.36±10.2*	1.67±0.8	8.93±9.4*
number of doses required to halt seizures	2.31±0.5		15.63±5.9		12.48±5.8	

Findings support the concept that control of seizures is more rapidly achieved with magnesium therapy than with calcium or barbiturate therapy.

**after treatment started; ( ) = number of patients*

retain almost 90% of a parenteral magnesium load.[95] Lesions of the small coronary arteries and resultant interference with conduction, possibly contributed to by magnesium deficiency, might also play a role.

Does the widespread use of therapeutic doses of vitamin D from early infancy contribute to the sharply increased incidence of arteriosclerosis and the emergence of such diseases as infantile endocardial fibroelastosis and the supravalvular aortic stenosis syndrome (such as those produced by experimental perinatal hypervitaminosis D) (Table 3)?[26,32,63,96-98] In a 1955 article on the changing character of pediatric practice in the second quarter of this century, it was suggested that "an unknown agent" might be etiologic in such new pediatric diseases.[99] The possibility that measures taken to abolish rickets might have been responsible for at least one of the new diseases, infantile hypercalcemia (with its cardiovascular sequelae), was proposed[99] and has been proved in children who are hyperreactive to vitamin D.[32] Often such children also show hyperlipidemia and hypertension.[26] Now that arteriosclerosis is being categorized as a pediatric disease, with not only vitamin D excess but magnesium deficiency known to be implicated in experimental cardiovascular lesions, attention should be paid to dietary imbalances and to metabolic abnormalities that can increase susceptibility to such imbalances. Marked metabolic abnormalities such as hyperreactivity to vitamin D or intestinal malabsorption of magnesium[85,100] are most readily identified. Perhaps, as has been proposed for vitamin D,[33] lesser degrees of abnormal metabolism of magnesium might lead to occult deficiency that might contribute to pediatric and adult cardiovascular disease. As an example, diabetes mellitus, a disease with a high frequency of vascular complications, has been associated with hypomagnesemia in both diabetic patients[101] and infants born to diabetic mothers.[76,78] Thus, the unknown agent may well be multifactorial—a combination of dietary imbalances to which those with metabolic aberrations that increase magnesium requirements are particularly vulnerable. Such individuals may be prone not only to rare new pediatric diseases but to the pediatric and later forms of cardiovascular disease.

Summary

The similarity of pathologic findings in infantile cardiovascular diseases to lesions caused by experimental magnesium deficiency suggests that suboptimal magnesium levels during pregnancy and in the neonatal period may contribute to congenital cardiovascular abnormalities. Dietary imbalances (such as high ratios of vitamin D, phosphate, and fat to magnesium) increase vulnerability to magnesium deficiency–induced cardiovascular damage in animals and might do so also in man, particularly in this country, where the magnesium intake is marginal or low and that of the other nutrients tends to be high. Neonatal hypoparathyroidism makes infants born to mothers with conditions that predispose to infantile hypomagnesemia especially vulnerable to hyperphosphatemia, a condition associated with neonatal hypoparathyroidism and enhanced by cow's milk formulas. It is speculated that such infants are prone not only to hypomagnesemic hypocalcemic tetany and convulsions but to early coronary arteriosclerotic lesions and possibly to arrhythmias that might lead to sudden infant death if the perivascular lesions involve conductive tissue. Later in infancy and in childhood, a low dietary magnesium to vitamin D ratio might contribute, as well, to more generalized atherosclerosis, hyperlipidemia, hypercalcemia, and hypertension.

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