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Overview: Recognizing the Problem of Magnesium Deficiency

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ABSTRACT

The magnesium (Mg) content of the usual American diet is less than the recommended dietary allowance (RDA). Excesses of some macro- and micronutrients interact with Mg, increasing its requirements. Marginal deficiency of Mg is not associated with hypomagnesemia, is not characterized by typical manifestations, and is thus difficult to diagnose. Serum or plasma Mg levels are held within narrow limits unless tissue levels are very low, or renal function is poor. Vulnerability to Mg deficiency increases during growth and development, pregnancy, when under physical or psychological stress, and during illness or its treatment that interferes with absorption or causes loss of Mg. Evidence of biochemical changes of early Mg deficiency is rarely sought, although the roles of Mg in many enzyme systems are recognized. The effects of Mg deficiency on metabolism, even in disorders caused by vitamin dependencies in which Mg is a co-factor, are largely unexplored. Deficiency of Mg is diagnosed confidently when the laboratory reports hypomagnesemia in patients with convulsions or arrhythmias. Without these signs, Mg levels are not often ordered, even in the presence of neuromuscular irritability such as respond to Mg repletion. Because Mg supplementation or Mg-sparing drugs protect against premature or ectopic heart beats and sudden death, to which diuretic-treated hypertensive patients are at risk, it is increasingly being advised that their Mg status be determined. The Mg, when added to potassium (K) supplements, improves their response to K-repletion. The implications of cardiovascular, renal and bone lesions, induced by long-term experimental Mg deficiency not severe enough to cause symptomatic hypomagnesemia, are rarely applied to clinical events. Because epidemiologic studies have disclosed higher incidences of ischemic heart disease, sudden (unexpected arrhythmic) cardiac death, and kidney stones in soft water geographic areas (with low Mg intakes) than in hard water regions, long-term intervention studies should be undertaken to determine whether higher Mg intakes are protective. The use of Mg as a parenteral drug has long been justified to control eclamptic convulsions and hypertension, its use to prevent and treat dysrhythmias of hypertensive patients receiving diuretics, of congestive heart failure or ischemic heart disease patients under cardiotonic treatment and of post-myocardial infarction patients is gaining attention. Whether the incidence of such life threatening events, and of predisposing conditions, can be reduced by raising the oral intake of Mg, requires further study.

INTRODUCTION

It is widely assumed that, because the American diet is rich in most nutrients, it must meet Mg requirements. However, metabolic balance studies with healthy volunteers under normal living conditions showed negative Mg balances on customary American intakes - especially among young men (112). Currently recommended dietary allowances (RDA) (91) for Mg were derived from analysis of these findings. Extensive dietary surveys have disclosed that, by this criterion, Mg intakes of many North Americans are suboptimal (infra vide). Studies of pregnant women, infants, young children and teen-

agers, show higher mg/kg requirements of Mg during anabolism (8,43,59,107, 112,135). The greater Mg need of pregnant women is considered in the RDAs; that of those growing and developing is not. The effects of other nutrients on its absorption and utilization is disregarded, as is the increased need during physical or psychological stress (86,107,109). Disease and drugs used in therapy, that interfere with intestinal absorption or increase renal loss of Mg, are gaining recognition as causes of Mg depletion. Acceptance of the need to determine the Mg status has been delayed by problems of methodology, by uncertainty as to normal ranges of serum or plasma Mg, and by the body's ability to maintain serum Mg within narrow limits despite subnormal tissue levels. Low serum Mg levels may be transitory, as the body mobilizes tissue sources, until serious loss ensues. Because plasma Mg usually rises slowly, even without Mg replacement, hypomagnesemia is often considered benign and not treated by Mg repletion. The pharmacologic efficacy of parenteral Mg, in controlling convulsions and hypertension of toxemias of pregnancy (67,84, 129,140), and its more recently accepted efficacy as a tocolytic agent (in impending premature birth (20,74,118) and in control of intractable cardiac arrhythmias (1,16,18, 32,34,53-55,105,117), has militated against acceptance by many physicians of Mg as a nutrient, dietary supplies of which may be suboptimal. Animal experiments and epidemiologic studies, however, indicate that adequate Mg intakes might protect against lesions that cause functional and structural changes which predispose to the lethal events (105,115). Far from general acceptance is the premise that oral Mg supplementation of the diet is justified, even in those with physiologic states and under stresses that increase needs, or with disease- or medication-induced loss.

REQUIREMENTS OF MAGNESIUM

As is true for all nutrients, optimal Mg intakes are the amounts that will maintain health: "physical and mental well being; freedom from disease, pain or defect; normality of physical and mental function" (12). However, it has been proposed that the RDAs should be lowered to reflect "minimal needs" (71): amounts below which symptoms and signs of deficiency are manifest and/ or other evidence of nutritional inadequacy can be elicited by appropriate tests. Early manifestations of Mg deficiency are rarely overt and difficult to detect. To lower the recommendations for Mg intake has inherent risks, as (experimental) Mg deficiency causes asymptomatic cardiovascular, renal, and bone damage, and subtle neuromuscular manifestations that can long precede the convulsions that are accepted as signs of Mg deficiency (9,30,97,105).

Protocols for metabolic balance studies, from which RDAs have been derived, have in common measurement of the studied nutrient in food consumed and in excreta, but otherwise differ. Those done with volunteers kept in a metabolic unit to keep environmental, as well as dietary intakes uniform, are essentially free of every day stresses. Subjects willing to accept such conditions for extended periods may be rather placid. Thus, such studies may yield values indicative of minimal requirements. Studies with free-living subjects are subject to errors of food consumption and excreta collection, but have the advantage of more normal life styles. Studies in which nutrient contents of duplicate self-selected meals and of excreta are determined are usually short-term, and subject to comparable errors. Among the variables that affect Mg needs are individual, dietary and environmental factors, none of which are considered in calculating RDAs. Metabolic balance studies are not applicable to determination of individual needs. Plasma or serum Mg, the easiest test to obtain, is not a reliable index of marginal Mg deficency, since serum levels are maintained at between 1.5-2.5 mEq/L, even when tissue levels may be sub-normal (35,113). Values as low as 1.5 mEq/L. are commonly

DIETARY FACTORS	HOST FACTORS	ENVIRONMENTAL FACTORS
Food	Physiologic Anabolism	Soil, Water
Processing;Refining	Growth & Development	Minerals
Water Added to Concentrates	Pregnancy & Lactation	Irradiation
Fiber Content	Convalescence	Latitude
Vitamin Excess	Aging	Season,Altitude
D Supplements & Additives	Genetic Defects	Stress Factors
Megadosage: B1, B6, C	Mg Malabsorption	Thermal
Mineral Excess	Renal Mg Wastage	Trauma:
Ca, Na, K, P	Membrane Transport	Accidental
Trace; Toxic	Vitamin B1, B6 Dependency	Surgery
Macronutrient Excess	Hormone Status	Noise
Sugar, Fat, Protein	Sex difference	Vibration
Rigid Dieting	PTH/CT	Emotion
Low Calorie	Catecholamines	Disease/Treatment
High, Incomplete Protein	Corticosteroids	Neoplasm
	Physical Activity/Personality	
	Muscle Building	
	Type:A,B	

TABLE I.: INTERACTION OF FACTORS THAT INFLUENCE MAGNESIUM REQUIREMENTS

listed as normal on laboratory reports, although they are low. Mg levels of red and white blood cells and skeletal muscle biopsy samples Mg are better better indicators of the Mg status, but each has drawbacks (35,105). The percentage retention of more than 40% of a parenterally administered Mg "load" indicates deficiency in patients with normal renal function.

Normal Young Adults: Analyses of balance data from worldwide studies disclose that healthy young women require at least 5 mg of Mg/kg/day to stay in balance; young men require more (112). Mg RDAs are thus 350 mg/d for men, and 300 mg/d for women. Pregnancy or lactation, and heavy exercise are estimated to increase Mg needs by 100 -150 mg/d (91). Dietary surveys have shown that Mg intakes in the U.S.A. are 4.5 to 5 mg/kg/d or less (66,70,75,79,107, 109,112,120,128): below the RDA. Self-selected meals of high school and college students contain less than the RDA, for Mg, provide the RDA for Ca, and more than the RDA for phosphorus (70,112,120, 128,135). Evaluations of Mg, Ca, P and vitamin D intakes, done since the turn of this century (Fig.1) (8,21,59,101,105,111) show that, unlike Ca which has

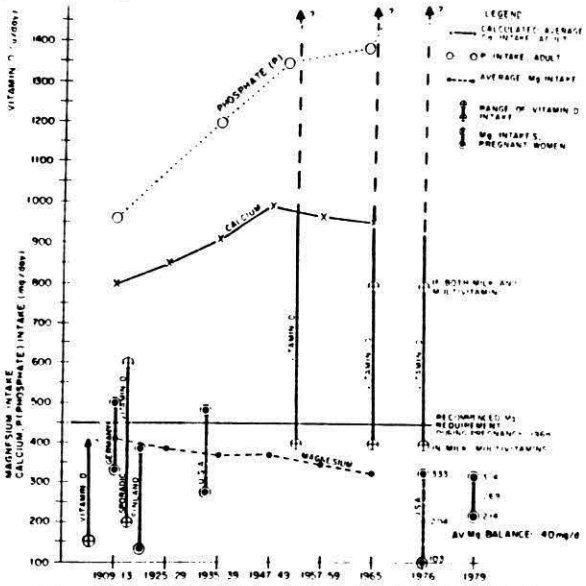

Figure 1. AVERAGE INTAKES OF Mg, Ca, P, & VITAMIN D IN THE 20th CENTURY; Mg BALANCES DURING PREGNANCY (105) (Reproduced by permission of Plenum Publ.)

which has slightly risen, and of P and vitamin D which have gone up sharply, intakes of Mg have tended to fall slightly (Figure 1).

How much Mg is required for normal growth and development and for muscle building during athletic training and body building, and to meet increased needs during illness and convalescence, and under conditions of stress has not been determined.

Effects of Pregnancy on Mg Requirements: Metabolic studies in pregnancy have shown negative Mg balances on many self-selected diets providing Mg intakes of 177-389 mg/day (8,21,59,101,105,111) (Fig.1). New tissue (maternal and fetal) is formed during pregnancy, necessitating maintenance of positive balances. Although the major accumulation of Mg is in the third trimester, fetal need for Mg is manifest throughout gestation (Table II, III)(21,136).

AGE OF FETUS (LUNAR MONTH)	MAGNESIUM (mg)
3	15
4	58
6	100
7	173
8	306
9	512
Term:	886

(from Coons et al, 1955[21])

TABLE II: FETAL MAGNESIUM

BODY WEIGHT OF FETUS (Grams)	MAGNESIUM (g/kg fat free) mg
32.5	.12
271	.15
787	.21
1966	.22
3050	.23
3105	.27
3500	760

(from Widdowson et al, 1951,1962 [136])

TABLE III: FETAL MAGNESIUM

Possibly, the long known response to Mg of hypertension and convulsions of toxemic pregnancy (67,84,140) reflects repair of Mg deficiency (105,129). In addition to the pharmacologic use of Mg during toxemias of pregnancy, the quieting effect of Mg on uterine spasms, has been applied to impending premature birth, as a tocolytic agent (20,51,74,118). This effect, like that in eclampsia, may reflect a deficiency that might contribute to abortions, miscarriages and premature births (4,65,105,111). Mg deficiency during fetal growth might contribute to antenatal cardiovascular disease in infancy that leads to the overt disease in adult life (104-106,108,111). This premise is suggested by the similarity of fetal and infantile cardiac and arterial lesions to those caused by experimental Mg deficiency (Table IV,104).

	INFANTILE ARTERIOSCLEROSIS	EXPERIMENTAL MAGNESIUM DEFICIENCY
INTIMA		←----------EDEMA, HYPERTROPHY----------→
SUBINTIMA	MUCOPOLYSACCHARIDES	
ELASTICA		←----------DEGENERATION, THINNING---------→
		←----------FRAGMENTATION----------→
	FATTY STREAKS ------CALCIFICATION----------→	
MEDIA		←----------EDEMA, HYPERPLASIA----------→
		←---------NECROSIS, CALCIFICATION---------→

TABLE IV INFANTILE ARTERIAL LESIONS AND THOSE CAUSED BY MAGNESIUM DEFICIENCY

Mg Requirements of Infants and Children: Infants at greatest risk of neonatal hypomagnesemia and thus in need of Mg supplementation, are those with low birth weights (60,125), whether due to prematurity or intrauterine growth retardation caused by placental abnormalities, such as are seen in pre-eclampsia and eclampsia, and in infants who have undergone surgery or other serious (Mg wasting) disease (137). Infants born to adolescents, whose own Mg needs may not be met (24), and to women who have had multiple births or frequent pregnancies (105) are also at risk of Mg deficiency. Infants of diabetic mothers, whose Mg status may be precarious (infra vide), may have hypomagnesemia and be difficult to manage since hypomagnesemic babies often

have secondary hypoparathyroidism, causing convulsive hypocalcemia - which responds better to Mg, which corrects both deficiencies, than to calcemic agents (6,36,63).

Early studies of infants, young children and adolescents suggest that the mg/kg amounts of Mg needed to sustain their growth may be much higher than the 6 mg/kg/d needed by the adult. It may be as high as 10-16 mg/kg/d in the adolescent, and possibly even more in the very young child (105). The retention of large amounts of Mg by young children and adolescents, and by convalescents, indicate the desirability of further study to determine Mg needs during normal anabolism.

Increased Magnesium Needs in Old Age: Dietary protein and fat of the elderly decline strikingly, especially in the seventh decade, while intakes of carbohydrate remain essentially unchanged, and thus disproportionately high (22,37). Their Mg intake also is rather low, and their susceptibility to Mg deficiency is intensified by diminished intestinal absorption and increased urinary output of Mg (19,58,72,77,110,124). Whether evidence that long-term Mg experimental inadequacy causes cardiovascular and renal damage is applicable to the chronic diseases of mankind, which are contributory to and intensified by the poor health of many elderly subjects is speculative. A clue to the poor adaptation to stress of the aging individual is provided by a study of rats maintained on a low Mg diet throughout their lives, and subjected to cold stress when they were old (50). Those surviving symptoms and signs of Mg deficiency during infancy adapted to the deficency, becoming symptom-free during their adult life. However, they had shorter lives than did the Mg-adequate rats, and were much less tolerant to severe stress, as manifested by cardiac necrosis and death.

Increased Mg Requirements Caused by Stress: Release of hormones that mediate response to stress (catecholamines and corticosteroids) is affected by the status of Mg and affects its needs. Stress-induced adrenergic over-activity increases oxygen demand (which causes egress of Mg from cells [86, 87]), and causes lipolysis. This increases free fatty acid- release, which causes inactivation of circulating Mg, thereby increasing its need (41,90). Catecholamine-secreting granules from nerve endings and the adrenal medulla secrete more catecholamines when suspended in a medium rich in Ca and poor in Mg than when in a high Mg/Ca medium, which reduces catecholamine release (11,26). Mg deficient rats have developed hypertrophy of the juxtaglomerular index, and increased levels of mineralocorticoids (15). There is evidence that stress of severe physical exertion and competition increases the need for Mg and that performance can be improved by its administration (25,44). The clinical arrhythmias of alcohol withdrawal and of myocardial infarction, which are stressful are managed better with addition of intravenous therapy with Mg (1,18,39-41,55,76,88,89,105,117,130,138) and which has a pharmacologic effect on cardiac irritability (46,121). It also repletes the Mg that is inactivated by stress-induced increased free fatty acids, and that might well have been inadequate before the acute event - certainly in alcoholics in withdrawal, and possibly also in the myocardial infarction victims (39, 41). Severe trauma also causes Mg loss (23).

Effects of Other Nutrients on Magnesium Requirements:

Macronutrients: The American diet commonly provides marginal amounts of Mg, but excesses of sugar, fat, protein and phosphate - each of which has intensified experimental Mg deficiency (29,105-107). Sugar loading in normal subjects, and its abnormal metabolism in diabetics is known to cause Mg loss (29,61,68,73,78). Excess dietary fat or fat malabsorption interferes with Mg absorption (72,105,107). High dietary phosphate, as in processed foods and carbonated beverages, or as phytate, has also interfered with utilization

of Mg (17,81,100,106,107). Interrelationships of protein in the diet with Mg are complex. Since Mg is a co-factor in the synthesis of protein and nucleic acids (3,101,109,127), high protein intake during anabolism increases needs for Mg. However, the amount and quality of dietary protein causes positive or negative Mg balance, depending on the relative amounts of each provided, the protein source, and the rate of growth or repair. Raising the protein intake of adolescent boys, from low to adequate, increased Mg retention (101). On the other hand, high protein diets of poor quality (i.e in diets for obesity reduction) has caused Mg loss (27,38).

Hard/Soft Water: The correlation of high cardiovascular death rates with soft water, and of low death rates with hard water (Fig.2, 105) is credited both to Ca and the Mg in the water. Each interferes with intestinal fat absorption, but analysis of their contrasting effects on cardiac rhythm and on tissue integrity, and substantial epidemiologic data support the premise that Mg is the protective cation in hard water (5,7,70,98,99,105,115). The evidence of protection by Ca in patients with low-renin hypertension, and by Mg of high-renin hypertensives (92,93), and of the low Mg levels in Type A subjects (49), who are subject to both cardiac disease and hypertension, indicates that genetic differences in Mg needs and distribution may explain some of the conflict.

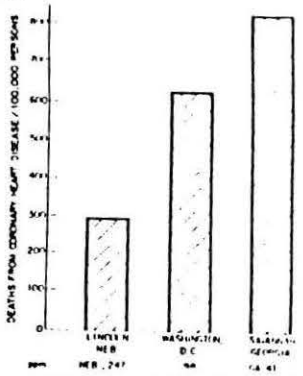

FIGURE 2. WATER HARDNESS & CARDIAC DEATH RATES

Calcemic Agents (Vitamin D and Calcium): Similarly Mg/vitamin D interrelations are complex (Fig.3) (105,106,109). Deficiency of vitamin D interferes with Mg retention, but vitamin D excess, which causes hypercalcemia, or Ca-loading of Mg-deficient animals intensify the lesions caused by Mg deficiency. Hypo- and hypercalcemia have each been seen in clinical Mg deficiency, the effect on Ca depending on the degree and duration of Mg deficiency. Vitamin

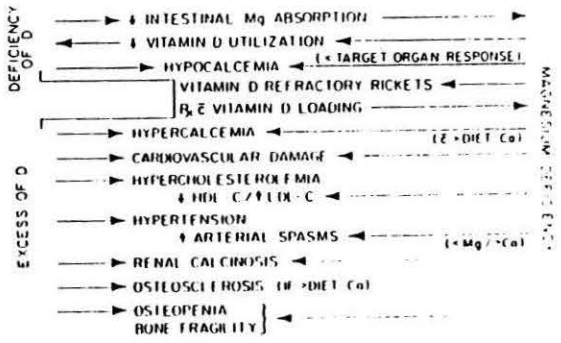

FIGURE 3. VITAMIN D AND MAGNESIUM INTERRELATIONS

Vitamin D supplementation and addition to many foods is widespread, so it is difficult to avoid ingesting more than prophylactic doses. Ca supplements are now widely promoted. Metabolic studies have indicated that moderately increased Ca intakes have not interfered with Mg (119), but further study of excess Ca and vitamin D in humans with long-term suboptimal Mg intake, or with hyperreactivity to vitamin D, deserve more attention.

Vitamins B6 and B1: Vitamins, the activities of which depend on Mg-activated enzymes, might increase Mg requirements when taken in high doses. Two such vitamins are pyridoxine and thiamin; many of their apoenzymes are Mg-dependent (Fig.2; Table V)(28,109). Deficiencies of pyridoxine and Mg are mutually enhancing; deficiency of one is partially responsive to the other (2,64). When both Mg and thiamin are deficient, as is seen in the alcoholic,

adequate response to thiamin requires Mg repletion (56,139).

Enzymes Dependent on Mg and Bl

pyruvate dehdrogenase
a-ketoglutarate dehydrogenase
transketolase
Mg-Dependent Bl Conversions

Mg++
Bl ---------->
Bl pyrophosphokinase
TPP (thiamin diphosphate)
Mg
TPP---------->
phosphoryl transferase
TTP (thiamin triphosphate)
---------->

Mg Deficiency - Bl Deficiency
Bl Repletion Alone -- Mg

TABLE V. MAGNESIUM & THIAMIN

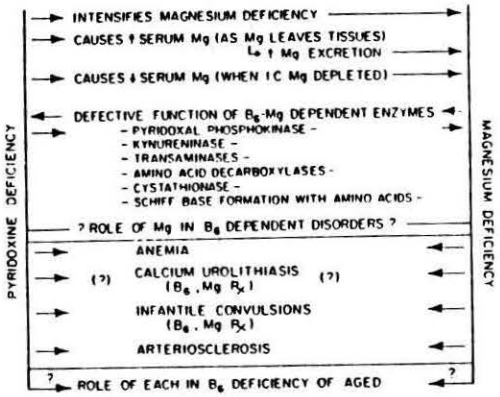

FIGURE 4. MAGNESIUM & PYRIDOXINE

Antioxidant Micronutrients: Less is known of interrelations of other vitamins and Mg, but as for vitamin C, high intakes of which are common, excesses have lowered tissue levels of Mg in guinea pigs (62). Vitamin E, among the micronutrients that affect free radicals, has activities that overlap with some of those of Mg (48,109,110).

Diseases That Increase Magnesium Requirements:

Alcoholism: One of the earliest clinical conditions recognized to cause symptomatic Mg deficiency is alcoholism (39,40); even moderate intakes, as in social drinking, increases the urinary output of Mg (39,40).

Gastrointestinal: Intestinal disorders that interfere with absorption, in general, such as infective diarrhea, inflammatory bowel disease, sprue or other forms of steatorrhea, or post-intestinal resection each causes fecal Mg loss (9,16,31,80). Familial Mg malabsorption is a genetic disorder that has caused refractory Mg depletion in infants (83,123). Protein-enriched-milk refeeding of starved children, who often have had severe diarrhea, has caused Mg deficiency leading to cardiac arrhythmias and death (14).

Cardiovascular Diseases: Gaining recognition is the role of magnesium loss in the arrhythmias and sudden cardiac deaths, associated with drugs used to treat hypertension and of congestive heart failure (18,32-34,52-55 75,96,130,132). Also receiving attention is the efficacy of Mg treatment of recent victims of myocardial infarction (1,41,55,76,88,89,105,117,133), who are likely to have had Mg deficiency and to lose Mg during the stress of the infarct. Such findings indicate the applicability to humans of the evidence that long-standing, low-grade experimental Mg deficiency can contribute to arterial and cardiac disease. The similarity of arterial lesions of "pure" experimental Mg deficiency to those seen in infants dying at birth or soon thereafter raises the possibility that the roots of the disease are in early life (104-106,111), perhaps even in gestation. The correlation of high rates of sudden unexpected cardiac deaths with low Mg intakes (i.e. in soft water, Mg from food) (5,7,98,99,105,109) and the possible role of low Mg with high blood pressure (5,57), supports the premise that those with predisposition to cardiovascular disease should be examined for Mg deficiency, which should be corrected if they are found to have high Mg retention. Diabetes Mellitus: It has long been known that diabetics have abnormal Mg metabolism (2,73,78), which is not surprising in view of the loss of Mg caused by high

sugar levels (61,68) and insulin's role in cellular Mg uptake - which has been applied to the treatment of MI patients treated with intra-venous glucose/insulin/potassium (GIK), addition of Mg converting the GIK to MAGIE (133). Substantial loss of cell Mg accompanies diabetic ketosis (73, 78). During insulin treatment, hypomagnesemia as well as hypokalemia can develop if Mg is not provided, with K, to maintain plasma levels as the cations shift into the cells. Metabolic balance studies of patients during recovery from diabetic acidosis disclosed that despite substantial Mg retention, cellular repletion had not been completed, as indicated by the continued positive balance at the end of a ten-day recovery period.

Qti.. Genetic Disorders: Those requiring most Mg (in the absence of diseases or treatment that alone or together interfere with Mg absorption or increase its renal loss) are those with isolated genetic Mg malabsorption (83,123), or with renal Mg wasting of unknown origin (47,94). It is possible that renal Mg wasting might be induced by calcemic therapy of hypocalcemia of severe Mg deficiency, which might cause intratubular calcium deposition of calcium, the crystals damaging the loop of Henle (where most filtered Mg is reabsorbed). Such renal damage has been seen in Ca-loaded Mg-deficient animals (13,105), and in a hypocalcemic infant whose underlying Mg depletion was detected the day of her death (126). However, the renal leakage of Mg, like Mg malabsorption, has been reported to be familial (47), and might also be a primary genetic defect.

Among the inborn errors of metabolism are vitamin-dependent diseases (102). Those characterized by abnormally high needs of vitamins that require Mg as a co-factor for their utilization and for activation of vitamin-dependent enzymes, such as thiamin and pyridoxine (supra vide) might be combined genetic abnormalities: of defects of membrane transport of the vitamin or of its conversion to its co-enzyme, and of Mg utilization or retention that might be partially responsible for the vitamin defect (109). This possibility has not yet been explored. However, thiamin-dependent encephalopathy of alcoholism (Wernicke-Korsakoff syndrome), that is associated not only with thiamin deficiency, but with alcohol-induced wastage of Mg, is unresponsive to B1 until Mg is repleted (109).

Therapy-Induced I...

Is Magnesium Supplementation Necessary?

Magnesium deficiency is likely to be silent, until it is severe. Its diagnosis is often missed, since serum (or plasma) levels tend to remain within limits that are commonly considered normal. A high index of suspicion is required, and special efforts should be made to detect occult deficiency - by measuring cellular Mg content, or determining percentage retention of parenteral loading doses. Since surveys have shown that the diets of most Americans do not meet the RDA, it is unlikely that at times of increased needs they will be met by self-selected diets. The possibility that RDAs for nutrients might be recalculated on the basis of "minimal nutritional needs" (71): the amounts needed to prevent overt manifestations of deficiency, has inherent risks, because recognized manifestations of Mg deficiency usually signal development of irreversible changes. Early neuromuscular, psycho-neurotic symptoms of early Mg deficiency that are recognized, particularly in Mediterranean countries (30), the syndrome being termed hypomagnesemic, normocalcemic latent tetany, are rarely diagnosed in this country (114). It has been correlated with mitral valve prolapse (45), a "new" disease.

Physicians have long been accustomed to considering Mg a "drug of choice" to correct hypertension and convulsions of eclampsia. Its efficacy in counteracting arrhythmias, also reported years ago, is gaining increased recognition for management of otherwise intractable cardiac arrhythmias. Not widely appreciated is the likelihood that both life-threatening conditions might be late manifestations of Mg deficiency, that are found in conditions associated with increased needs. Genetic differences in requirements of Mg may explain the disagreement as to whether Mg deficiency contributes to a wide variety of diseases, and whether supplementation with Mg will prevent or alleviate some of the conditions that resemble manifestations of Mg deficiency in animals, or that respond to pharmacologic doses.

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DISCUSSION

INQUIRER: Iain Thornton, Imperial College, London, United Kingdom

Q: Have original or national differences in dietary Mg intake been recognized and linked to good epidemiological data?

A: The first epidemiologic clues to the protective role of Mg against cardiovascular disease were provided by J. Kobayashi in Japan (Ber. Ohara Inst. 11:12, 1957), who reported that the incidence of apoplexy was higher in soft than in hard water areas. In the United States, H. Schroeder reported that among white middle-aged and elderly men the death rates from ischemic heart disease was significantly higher in states and cities with soft water than in those with hard water (J.A.M.A. 95: 172, 1960; J. Chron. Dis. 172: 1902, 1960; J. Chron. Dis. 12:586, 1960; J.A.M.A. 195:125, 1966). In his 1960 publications, he correlated the low death rates with hardness of water; in 1966 he reported that the correlation was much stronger for Mg ($p<0.0005$) than for Ca (<0.02) - the two major cationic constituents of hard water. Even where the hardness of water derives largely from Ca (in England) hearts of men under 60 years old who died of accidents in Glasgow - soft water - had evidence of small myocardial scars and lower cardiac Mg than in London - hard water (Crawford & Crawford, Lancet 1:229, 1967). Comparable findings from Ontario, where accident victims in soft water cities had 7% less myocardial Mg than in hard water cities in contrast to their higher Ca levels and insignificant differences in other cations, supported the premise that it is the Mg that is protective (T.W. Anderson et al, Canad Med Assoc J 113:199, 1975). Finland, where the dietary Ca and salt is high and that of Mg is low, as is the water and soil content), has the highest cardiovascular death rate of young and middle aged men (Karppanen & Neuvonen, Lancet 2: 1390, 1973). Marier, who reported early on the epidemiologic evidence on hard water and heart disease (Brit Med J 2: 686, 1963), has published many analyses and reviews as to the protective effect of Mg (Magnesium 1:3, 1982; 5:1, 1986).

INQUIRER: Milton W. Meyer

Q: Is the Mg loss of alcoholics due to the alcohol or poor diet of alcoholics?

A: Both. Studies with normal subjects given a moderate amount of alcohol showed that it markedly increases urinary Mg excretion (Kalbfleisch, Lindeman, Smith: L Lab Clin Med 48: 833, 1961; McCollister, Flink, Lewis: Am J Clin Nutr 12: 415, 1963).

INQUIRER: T.W. Perry, Purdue University, West Lafayette, IN

Q: What is the danger of twice the recommended daily allowances of magnesium?

A: Unless the subject has substantial loss of renal excretory function, there is no risk, even to pharmacologic dosage of Mg, since the kidneys normally excrete amounts of Mg above the renal threshold rapidly - keeping the serum Mg levels stable. Practical demonstration is the common use of antacid and cathartic doses of Mg, as well as the imbibing of mineral spring waters rich in Mg (i.e. Epsom; Vittel, etc.) without other than the effects for which the high doses of Mg were taken.

INQUIRER: M.D. Waters, EPA, Research Triangle Park, NC

Q: Would you say what types of "integrative bioassays" you are using?

A: My findings derive from analyses and correlation of data from published research reports - clinical, epidemiologic, and experimental (human and animal) to which I have added clinical verification from hospital investigations.

INQUIRER: Nord L. Gale, University of Missouri-Rolla, Rolla, MO

Q: Thank you for a beautiful presentation! Would you care to comment on the possible exacerbation of Mg deficiency problems in cases or populations where <u>lead</u> may be elevated?

A: I am aware of no studies specifically on this point. Many years ago, A.R. Krall was interested in Pb/Mg interrelations, and reported the partial repair of Pb-damaged mitochondria by addition of Mg. He may be able to provide the information you want. The use of EDTA, in the treatment of Pb-toxicity, is likely also to deplete the body of Mg, unless the Mg withdrawn is repleted.