MAGNESIUM DEFICIENCY IN THE PATHOGENESIS OF DISEASE

Early Roots of Cardiovascular, Skeletal, and Renal Abnormalities

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Mildred S. Seelig, M.D.

MAGNESIUM DEFICIENCY IN THE PATHOGENESIS OF DISEASE

Early Roots of Cardiovascular, Skeletal, and Renal Abnormalities

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To my beloved husband

Alexander Seelig

without whose encouragement, understanding,
and support this book would not have been written

Preface

There is a large and rapidly growing body of literature on the importance of magnesium in biochemical and physiological processes. There is also much evidence that magnesium deficiency, alone and in combination with agents that interfere with its utilization, is associated with functional and structural abnormalities of membranes, cells, organs, and systems. The manifestations of the changes caused by magnesium deficiency depend upon its extent and duration and on variable factors. Among the conditions that increase the risk of magnesium deficiency are (1) metabolic factors that affect the absorption, distribution, and excretion of this mineral; (2) disease and therapy; (3) physiologic states that increase requirements for nutrients; and (4) nutritional imbalances. Excesses of nutrients that interfere with the absorption or increase the excretion of magnesium—such as fat, phosphate, sugar, and vitamin D—can contribute to long-lasting relative magnesium deficiency. All have been implicated in several of the diseases considered in this book. Whether their influence on the need for magnesium is a common denominator remains to be investigated further.

Unfortunately, means of diagnosing clinical magnesium deficiency of a lesser degree than that associated with overt signs such as convulsions or cardiac arrhythmias or other electrocardiographic changes are not readily accessible. Plasma magnesium levels are unreliable as an index of its cellular inadequacy. More complicated means of evaluating the magnesium status are considered in the Appendix, as are their limitations and need for convenient determinants. Until magnesium clinical methodology is improved and made available, the importance of correcting magnesium deficiency in man's diet and of preventing intensification of a deficit when needs are increased by physiologic or pathologic processes and drugs will have to be inferential—based on experimental and epidemiologic observations. Because magnesium has pharmacologic activities that have been recognized for many years, demonstration of the correction of abnormal acute neurologic and cardiac signs (even though such signs are characteristic of acute magnesium deficiency) are not readily accepted as evidence that magnesium deficiency can contribute to diseases in which such magnesium-responsive signs are seen. With notable exceptions, there has been clinical neglect of magnesium in most medical centers and certainly in private practice. This is unfortunate because many of the pathologic changes pro-

duced by experimental magnesium deficiency or loss resemble many of those of chronic diseases that are responsible for intractable medical problems.

This book develops the premise that magnesium deficiency during gestation is more common than generally believed and that it may be contributory to some disorders of pregnancy and infancy. It draws parallels between cardiovascular and skeletorenal lesions of infancy and childhood and those produced by magnesium deficiency—especially when intensified by dietary excesses of vitamin D and of phosphate, which are commonly consumed in the United States and other Occidental countries. It suggests that the most severe lesions (of magnesium deficiency ± vitamin D ± phosphate excess) resemble those of some congenital abnormalities. Lesions that develop later in infancy might provide the nidus for chronic cardiovascular and renal diseases of later childhood and adult life. Epidemiologic evidence is considered, having provided inferential evidence that magnesium deficiency (as in soft-water areas) contributes to the higher rate of sudden cardiac deaths (than in hard-water areas). Although differences in trace mineral and calcium contents of hard and soft water are also considered contributory, the most convincing evidence is that magnesium in hard-water areas is protective. Such a premise is subject to criticism because there are always concomitant factors that cloud the issue. Other dietary and environmental, as well as genetic, differences make it unlikely that there is a single provocative factor.

This book constitutes a plea for the objective examination of the evidence and for the exploration of the possibility that the prophylactic use of magnesium—especially in geographic areas where the intake is low, in families whose members have a high incidence of cardiovascular disease, and in high-risk individuals (e.g., diabetics and patients with a personal history of cardiac or vascular disease)—might be effective. Reevaluation of the use of vitamin D and of phosphate in foods is justifiable. The use of magnesium in the treatment of cardiac and renal diseases has been claimed by some investigators to be an important adjunct to therapy. More controlled studies should be done to obtain further evidence as to the extent to which experimental evidence and pilot clinical trials, indicative of benefits produced by magnesium, are applicable to more extensive treatment and prevention of human disease.

The substantial data on drugs (such as diuretics, cardiotonics, and antibiotics) that cause magnesium loss or inactivation are referred to only in the context of the theme of this volume and are so indexed. Further development will be provided elsewhere.

Appreciation is expressed to Harriet Nathan, May Becker, Marie Bennett, and Doris Wallace for typing the manuscript and to Dr. A. R. Berger for approving this employment of the secretarial staff of the Medical Service of Goldwater Memorial Hospital.

Mildred S. Seelig

New York

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1
Introduction: Consideration of Epidemiologic Factors

1.1. Ischemic Heart Disease

The most alarming trend in the past half-century has been the sharp increase in sudden deaths from ischemic heart disease (IHD), particularly in middle-aged men, and the increasing number of younger men who suddenly develop myocardial infarctions, cardiac arrhythmias, or arrests. That men in the prime of life are thus afflicted is the dramatic and tragic tip of the iceberg. Underlying these catastrophes is the widespread increase in incidence of atherosclerosis in young age groups, and in myocardial hyperexcitability and cardiomyopathy without notable coronary atherosclerosis. It is proposed that magnesium deficiency or loss may be a common etiologic factor in the increased incidence of sudden infant deaths, infantile myocardial infarction and arteriosclerosis, and the disease that becomes manifest later in life. It is also suggested that magnesium deficiency might also cause or predispose to some skeletal and renal diseases, all of which can coexist.

The cardiac problem in men has been deemed of sufficient magnitude as to be termed an epidemic that has been increasing, particularly since the middle 1930s. It has led to widespread institution of therapeutic and prophylactic regimens on the basis of suggestive findings. For example, young women have a significantly lower incidence of ischemic heart disease than do young men (Fig. 1-1). Because their α/β-lipoprotein ratios differ from those of the more susceptible young men and especially from those of patients with peripheral or coronary atherosclerosis, there was a period during which estrogens were widely used in the treatment of patients with myocardial infarctions and given prophylactically to high-risk (hyperlipidemic) men and postmenopausal women. This approach has been largely discontinued, predominantly because of the resultant increase in risk of thrombosis. Another approach that was given a trial period was administration of excesses of unsaturated fatty acids; the incidence of atherosclerosis and IHD is lower in countries where more vegetable oils than saturated animal fats are consumed. A modification of the fatty-acid-supplement regimens that has been receiving extensive clinical trial is to

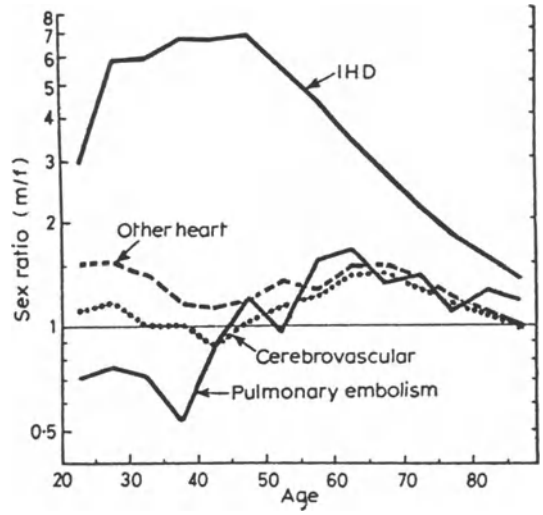

FIGURE 1-1. Ratio of male to female cardiovascular death rates by 5-year age groups based on death rates for England and Wales. (From TW Anderson: *New Scientist* 9:374–376, 1978.)

replace saturated with unsaturated fats. This approach has lowered blood lipids, but not the incidence of IHD. Because altering fat intakes of patients with established hyperlipidemia and atherosclerosis has not reduced the mortality from IHD, it has been recommended that the time to institute such a dietary modification might be in early infancy, a suggestion that has been disputed.

1.2. Concomitant Cardiovascular, Skeletal, and Renal Diseases

Among women, the incidence of atherosclerosis and IHD increases with age, especially after the menopause, often in association with osteopenia or with calcific renal disease. The combined problem of bone wasting and extraskeletal calcification (particularly renal and cardiovascular) is also encountered in renal osteodystrophy and in other conditions associated with hyperparathyroidism and phosphate treatment of hypercalcemia.

Rarer forms of osteopenia, usually found in association with cardiac anomalies, arteriosclerosis, and renal calcinosis, are seen in infants of low birth weight, or who have osteogenesis imperfecta or hypophosphatasia. The more common, but not widely known, arteriosclerosis and IHD of early infancy is also usually accompanied by renal calcinosis, as is the later form that is accompanied by hyperlipidemia, hypertension and atherosclerosis. The latter type—some forms of which are associated with aortic and pulmonary stenoses and atresias, and with endocardial fibroelastosis—has been attributed to hypervitaminosis D (Seelig, 1969b; Seelig and Haddy, 1976/1980) which contributes to loss of magnesium. These conditions are

stressed in this volume because they support the supposition that atherosclerosis (and some renal and skeletal diseases) have their roots early in infancy and have put the onus on the absolute or conditioned magnesium deficiency that has become a problem during this century.

Magnesium plays an important role in maintaining the integrity of the myocardium, kidneys, and bone. Its deficiency has been shown to cause cardiomyopathy in several animal species, and to intensify myocardial lesions caused by a variety of modalities. Its deficiency has caused arteriosclerosis and has intensified formation of atheromata, or arteriosclerosis, thrombosis, and even myocardial infarction, induced by atherogenic diets, high intakes of vitamin D, calcium, phosphate, and fat. Its deficiency has caused renal lesions and intensified damage produced by vitamin D, calcium, and phosphate. And its deficiency has been implicated in some forms of bone damage. Magnesium supplementation has prevented or reversed some of the lesions in the experimental models and been used clinically in cardiovascular disease and urolithiasis.

1.3. Changing Magnesium, Vitamin D, and Phosphate Intakes

Examination of the changing nutritional intakes in America, particularly from the middle 1930s is disconcerting in light of these experimental findings. Although magnesium intakes have been gradually falling since the beginning of the century, there were sharply increased intakes of nutrients that increased its requirements [particularly high vitamin D and phosphorus intakes (Seelig, 1964, 1971) subsequently (Fig. 1-2)]. The rise in vitamin D intake began when the addition to each quart of milk of a sufficient amount (400 IU) to cure, rather than merely to prevent, rickets became widespread from the mid 1930s and was made mandatory in most states from the 1940s to 1950, either replacing cod liver oil, or taken in addition to it (Baldwin, 1953; Seelig, 1969b, 1970b). Fortification of many foods in addition to milk, including milk flavoring, oleomargarine, breakfast cereals, or "substitutes," led the Committee on Nutrition of the American Academy of Pediatrics to express concern about the total daily intake of vitamin D in the United States, which they calculated might range from 600 to 4000 IU/day from marketed fortified products (Table 1-1). A survey of 1000 Canadian children from 1 week to 5½ years of age showed that 70% consumed more than 400 IU, and 30% consumed over 1000 IU of vitamin D daily (Broadfoot *et al.*, 1972). Table 1-2 depicts the sources of vitamin D among those receiving over 1000 to 1800 IU of vitamin D per day. The major source of phosphorus derives from soft drinks that contain phosphoric acid, the consumption of which has been rising markedly in the last quarter of a century (Henderson, 1972; Lutwak 1974).

Although it is generally believed that the rise in blood lipids is due to increased intakes of saturated fats during this century, and that sugar consumption has also increased substantially, comparison of per capita intakes from 1909 to 1965 shows relatively minor changes (Fig. 1-3). The average daily fat intake rose from 112 to

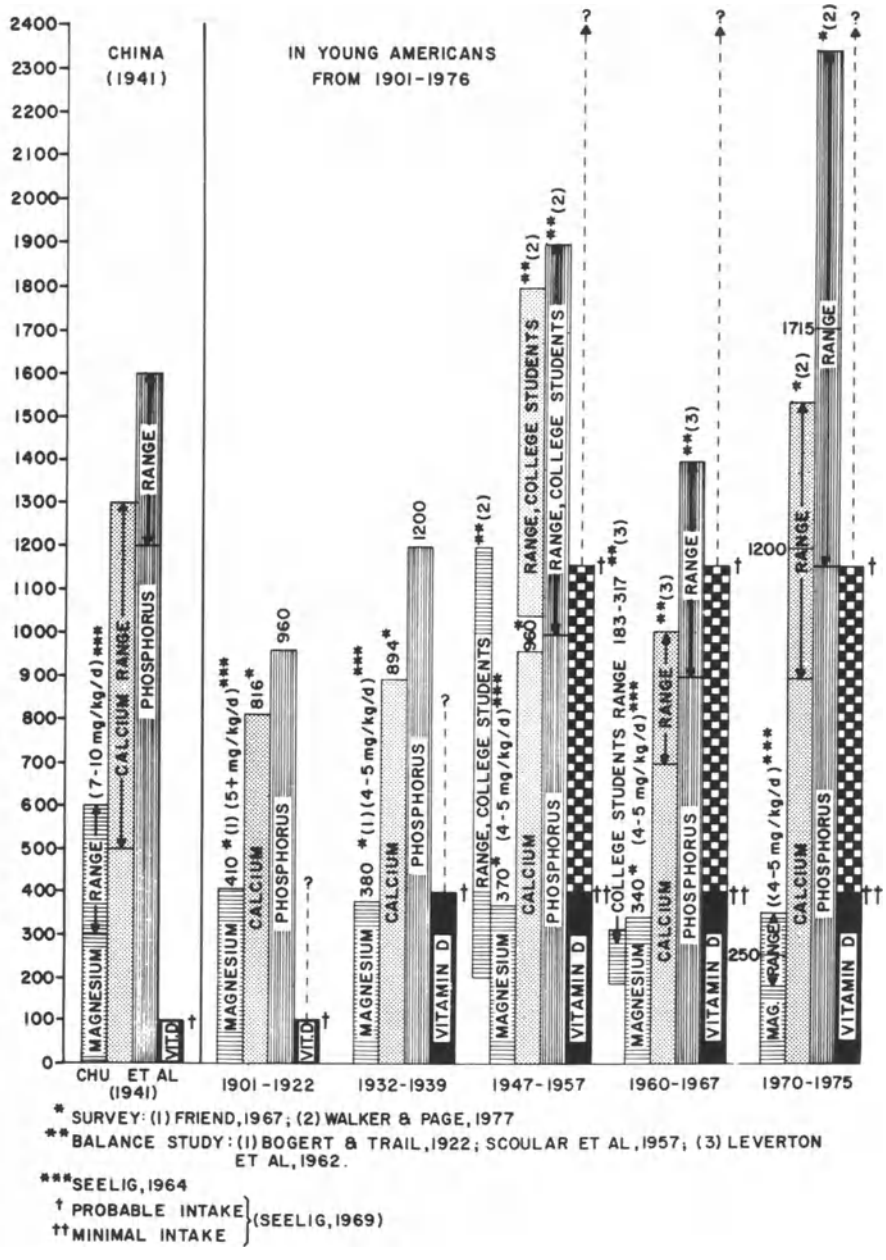

FIGURE 1-2. Changes in intakes of magnesium and nutrients that increase magnesium requirements (calcium, phosphorus, vitamin D).

TABLE 1-1. Hypothetic Total Daily Intakes of Vitamin D[a]

Age of child	Intake	Amount of vitamin D contributed by individual food (IU/day)[b]									Total intake (IU/day)	
		Vitamin supplement	Milk, liquid	Milk, evaporated	Milk, powder	Milk, flavoring	Margarine	Breakfast cereal	Special breakfast drink	Special candy bar or biscuit	Average	High
						A. Children in United States						
6 mo	Average	400		400							800	
	High	1000		400							600	1400
3 yr	Average	(1000)	300				100	200			(1600)	
	High	1000	400			450	350	400		(400)		2600 (3000)
8 yr	Average	(400)	400				200	200			800 (1200)	
	High	1000	400			600	500	400	(1000)	(800)		2900 (4700)
						B. Children in Canada						
6 mo	Average	400		800							1200	
	High	1000		1000								2000
3 yr	Average	(400)	25				275			(100)	300 (800)	
	High	1000			800	450	400	400	200	(150)		3250 (3400)
8 yr	Average	(400)	25				275	400			700 (1100)	
	High	1000			800	600	500	800	400	(150)		4100 (4250)

[a] From the Committee on Nutrition of the American Academy of Pediatrics (1963).
[b] When values appear in parentheses, total intake of vitamin D has been calculated twice; once including and once excluding these values.

TABLE 1-2. Vitamin D Intake Pattern of All Children Comsuming 1000–1799 IU and 1800 + IU Daily

	Average daily intake of vitamin D (IU) for children receiving				
			Supplement and fortified foods		
Source	Age (months)	Fortified foods only (1000–1799 IU)	1000–1799 IU	1800 + IU	Supplement only (1000–1799 IU)
Vitamin supplement	0–6		526 (56)	1200 (5)	1000 (9)
	7–66		1045 (196)	1426 (17)	1000 (24)
Milk	0–6		663 (56)	800 (5)	
	7–66	314[b] (4)[a]	71 (27)	317 (8)	
Margarine	0–6				
	7–66	442 (7)	85 (91)	166 (9)	
Cereal	0–6				
	7–66	478 (6)	173 (149)	182 (10)	
Milk flavorings	0–6				
	7–66	35 (4)	21 (81)	15 (6)	
Biscuits	0–6		1 (2)		
	7–66		5 (8)	28 (3)	
Fruit drinks	0–6				
	7–66		4 (5)		
TOTAL AVERAGE INTAKE	0–6		1190 (56)	2000 (5)	1000 (9)
	7–66	1269 (7)	1404 (196)	2134 (17)	1000 (24)

[a] The number of children receiving vitamin D from the source specified in the left margin is shown in parentheses.
[b] Average intake of vitamin from this source for all children in the intake group.

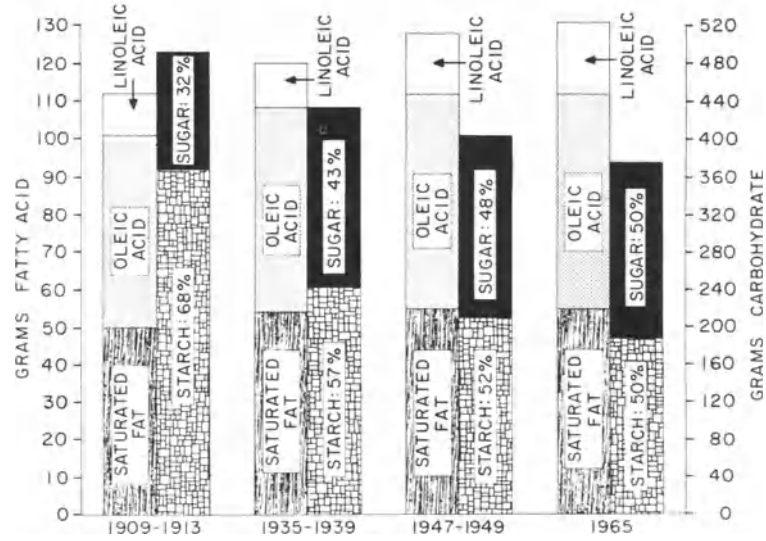

FIGURE 1-3. Fatty acid and carbohydrate intakes per capita per day from 1909 to 1965 (United States). (Adapted from Friend, 1967.)

132, but most of the increase has been in unsaturated fatty acids. The total carbohydrate intake dropped from 492 to 374, so that the greater percentage increase of sugar in 1965 reflects an increase of about 40 grams daily. Probably the sugar intake has risen more since the 1965 value (Fig. 1-2) among those who drink larger quantities of sugar-sweetened, phosphorus-containing soft drinks.

Largely disregarded is the possibility that the hyperlipidemia associated with atherosclerosis might be caused by hypervitaminosis D, which also causes hypertension (Linden, 1977; Seelig and Haddy, 1976/1980), as well as the more widely recognized complications; cardiovascular and renal damage, and hypercalcemia (Seelig, 1969b). Much of the clinical data on the cardiovascular, skeletal, and renal damage caused by vitamin D derives from the use of massive doses of vitamin D a quarter of a century ago in the treatment of such diseases as rheumatoid arthritis, and from the lesser overdosage of European children at a time when administration of up to 4000 IU/day was not uncommon (Table 1-3; Seelig, 1969b). The sharp rise in vitamin D intake depicted for the 1947–1957 segment of Fig. 1-1 is presumed because of the probable consumption of large quantities of milk by the college students studied—an impression suggested by their high calcium intake (Scoular *et al.*, 1957), in contrast to the lower intake noted in a general diet survey (Friend, 1967). Since the amount of vitamin D needed by most adults is considered so small as to be met by exposure to sunlight and by ingestion of natural (unfortified) foods (Food and Nutrition Board, 1968), such high intakes must be considered well into the toxic range. As long ago as 1932, L. Harris reported that in the human, the toxic dose of vitamin D is not far removed from the therapeutic (antiricketic) dose. Stewart (1964) reported that there is a narrow toxic–therapeutic ratio. Furthermore, even most infants are protected against rickets by as little as 100 IU of vitamin D daily (Fraser, 1967), whereas a survey of young Americans showed that 50% ingested 400–800 IU daily, 10% usually consumed over 1000 IU daily, and occasionally as much as 2900 IU were taken (Dale and Lowenberg, 1967). Epidemiologic data have correlated moderately high vitamin D intake with increased incidence of myocardial infarction, renal calcinosis, and urolithiasis (Linden, 1974a,b). In

TABLE 1-3 (A). Fortification of National Dried Milk[a]

Date	IU vitamin D per dry ounce	Recommendation by
1945	280	Ministry of Health
1953	500	Ministry of Food
1957	90–100	Ministry of Health

TABLE 1-3 (B). Calculated Daily Intake of Vitamin D (1956)[a]

1½ pints dried milk (460 U/dry oz.)		1725 IU
1 ounce cereal (1000–1500/dry oz.)		1000–1500 IU
1 tsp. cod liver oil		700–800 IU
	TOTAL:	3525–4025 IU

[a] From Report of Subcomm. of Brit. Ped. Assoc., *Lancet*, 1956.

northern Norway, where intake of natural foods rich in vitamin D is common, the incidence of hypercholesterolemia and susceptibility to sudden death from ischemic heart disease and to calcific renal diseases, two conditions which are often found in the same patient (Linden, 1972, 1975/1977; Westlund, 1973), seems to be related to the amount of vitamin D ingested and to the individual sensitivity to solar irradiation. Since magnesium deficiency is also associated with abnormal lipid distribution, and vitamin D excess causes magnesium loss, interrelations of protracted high intakes of vitamin D with magnesium requirements, and with the cardiovascular and renal lesions of each imbalance, deserve study (Seelig, 1977).

Like magnesium deficiency and hypervitaminosis D, excess phosphate has also been implicated in cardiovascular, skeletal, and renal damage. The nature of the pathologic changes produced by dietary excesses of phosphorus depends upon its ratios to both calcium and magnesium. Figure 1-2 shows that the phosphorus intake increased sharply in the college studies during the periods analyzed in 1947–1957 (Scoular *et al.* 1957), and in the most recent survey of college diets (Walker and Page, 1977). The lower phosphorus level entered in the 1960–1967 block of columns derives from an extensive metabolic balance study in several colleges (Leverton *et al.*, 1962). One can speculate that during these strictly controlled periods there was likely to have been less consumption of soft drinks containing phosphoric acid than during the self-selected dietary intakes reflected in the college diet surveys.

The recommended phosphorus/calcium (P/Ca) ratio is 1.5/1 (U.S. Department of Agriculture Report, 1972). In 1932–1939, the P/Ca ratio was about 1.2/1; it was estimated to be rising to as much as 4/1 among those who substitute sodas for milk (Lutwak, 1974). This shift in ratios was stressed as potentially harmful to bones, as a result of secondary hyperparathyroidism, on the basis of the effect of the osteopenia produced by comparable P/Ca dietary ratios in several species of animals, up to the monkey (Krook and Barrett, 1962; Krook *et al.*, 1963, 1971; Henrı .son *et al.*, 1970; Draper *et al.*, 1972; Krishnarao and Draper, 1972; Krook *et al.*, 1975).

However, the most recent dietary survey of college diets from fifty colleges (M. Walker and Page, 1977) showed that the mean P/Ca ratio was about 1.5/1, both phosphorus and calcium intakes having risen to 1200 and 1700 mg/day, respectively. What had dropped was the magnesium intake—to a mean of 250 mg/day. Such diets provide dietary ratios of Ca/Mg and P/Mg of almost 5/1 and almost 7/1, respectively. Since an excess of either phosphorus or calcium has been shown to increase magnesium requirements and to intensify signs of magnesium deficiency (Reviews: Seelig, 1964, 1971), such a dietary pattern—particularly when accompanied by high vitamin D and phosphate intakes by many—can be expected to produce either absolute or relative magnesium deficiency.

1.4. Sex Difference in Magnesium Retention

Analysis of published metabolic balance studies (such as are done to establish a nutritional requirement, an amount sufficient to maintain equilibrium) has shown that young men require more magnesium in mg/kg/day than do young women (Fig. 1-4) (Seelig, 1964). The studies analyzed had been obtained from throughout the world, and showed that young Americans tended to ingest less magnesium on self-

MAGNESIUM INTAKE MG / KG / DAY		< 4.0		4.0-4.9		5.0-5.9		6.0-6.9		7.0-10.0		> 10.0	
SEX		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
TOTAL NUMBER DAYS IN ALL STUDIES		658	781	861	1,082	656	272	499	211	1,099	54	271	16
NUMBER OF BALANCE PERIODS REPORTED		105	146	167	176	95	53	55	32	59	6	43	4
PERCENTAGE OF BALANCE PERIODS	0	75	63	54	56	46	40	22	12	22	33	14	0
	NEGATIVE +15	83	73	72	55	58	53	31	28	34	50	14	0

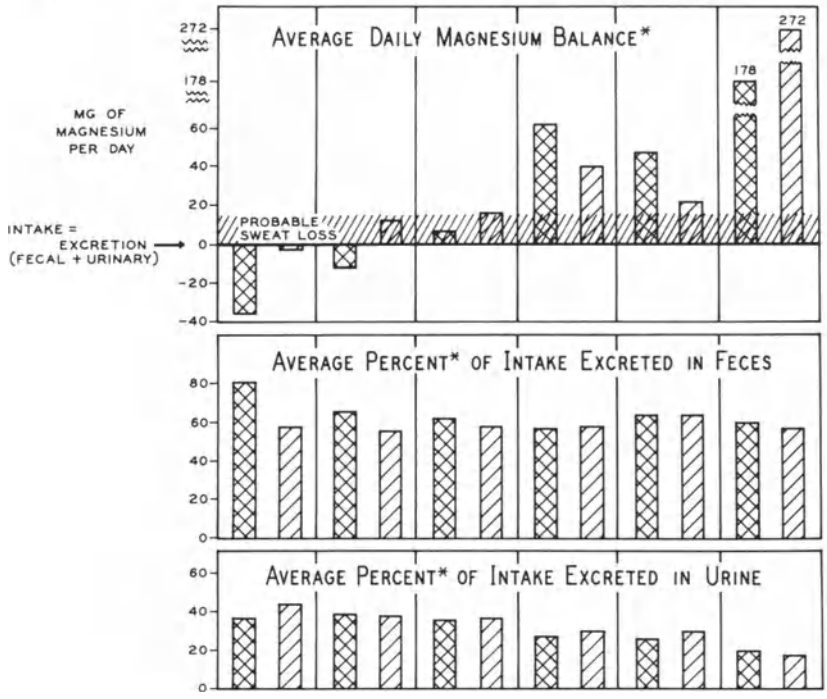

FIGURE 1-4. Influence of sex on magnesium balance and on percentage of intake excreted at different intakes of magnesium. *Figures are weighted by multiplying by number of days in each study. Only balance periods in which mg/kg intake can be calculated are included in analysis. (From MS Seelig: *Am J Clin Nutr* 14:342–390, 1964.)

selected diets than did Orientals and, on average, tended to be in negative balance. This was particularly so for the young men, who on the average excreted more magnesium than they ingested on the typical American intake of 4–4.9 mg/kg/day. Young women on that typical intake, on the other hand, tended to remain in equilibrium. The typical magnesium intake of the Orientals studied was between 7 and 10 mg/kg/day, and positive balance or equilibrium was the rule. In deriving the recommended magnesium intake from the data analyzed, the intake was selected at which equilibrium or positive balance was reached in at least three-fourths of the subjects. On this basis, the minimal daily requirement is 6 mg/kg/day. For a 140-lb woman, this comes to 385 mg of magnesium daily; for a 185-lb man, at least 500 mg/day. Americans, and others in industrialized countries, tend to ingest diets rich in other nutrients (fat, protein, sugar, phosphorus, and vitamin D), all of which increase magnesium requirements (Seelig, 1964, 1971; Lindeman, 1976/1980). In addition, moderate to heavy ingestion of alcohol (even as "social" drinking) is not

uncommon, and alcohol is magnesuretic (McCollister *et al.*, 1958, 1963; Kalbfleisch *et al.*, 1963). Thus, a magnesium intake of 7–10 mg/kg/day might be preferable. On this basis, a 185-lb man might require 580–800 mg/day of magnesium, probably approximately twice as much as his diet normally delivers. Possibly a woman (unless she is pregnant or lactating) requires somewhat less. The most recent survey of college students (from 50 colleges) shows that less than the modest officially recommended amount [300 mg for women; 350 mg for men (Food and Nutrition Board, 1974)] is the amount usually ingested (M. Walker and Page, 1977). Actually, the mean daily magnesium intake of the college students (250 mg) may well be no more than half the amount required by the young women; it may be as little as one-half to one-third the amount needed by large, athletic young men. In contrast to their inadequate magnesium intake, they ingest one and a half times the recommended amount of calcium and twice the phosphorus allowance. Consumption by young college women of diets that provide suboptimal amounts of magnesium is not unique to the 50 colleges surveyed. N. Johnson and Philipps (1976/1980) surveyed the diets of pregnant women from different economic brackets, and found that their magnesium intakes ranged from 103 to 333 mg/day, with an average of 204 mg daily, an amount grossly inadequate for pregnant women. Ashe (1979) confirmed the inadequacy of prenatal magnesium intakes of 10 healthy white women from private practices in Tennessee by 7-day metabolic balance studies done at intervals throughout pregnancy. Their mean daily magnesium intakes were only 60% the recommended 450 mg/day, and mean balances were −40 mg/day. Only 3 of the 47 periods were positive. The investigators suggested that high calcium, phosphorus, and protein intakes might have intensified the severity of the negative magnesium balances. The significance of such low magnesium intakes during gestation, as regards the cardiovascular, skeletal, and renal status of infants of women with gestational magnesium deficiency, is considered in Part I of this volume.

Now that high fiber- (and phytate-) containing diets are increasingly being recommended, the effect of such diets on a magnesium intake that is otherwise meager should be explored. Review of metabolic studies of magnesium utilization by subjects on diets rich in phytates—brown bread, brown rice, oatmeal, or white bread to which phytate had been added—showed poor percentage absorption of the magnesium, particularly when the diet was first changed (Seelig, 1964). After several weeks on the phytate-rich diet, the absorption of magnesium tended to improve (A. Walker *et al.*, 1948; Cullumbine *et al.*, 1950; Hathaway, 1962). McCance and Widdowson (1942a,b) found that addition of phytate to white bread caused greater fecal magnesium excretion, and removing phytate from brown bread greatly improved magnesium absorption. Reinhold *et al.* (1976) have recently confirmed these observations, not only for magnesium but for trace metals. Thus, the higher magnesium content of phytate-containing whole grain products may not be a reliable source, in terms of availability of magnesium. Whether adaptation to the phytate ingested, on its continued inclusion in the diet, will result in better utilization (as suggested in the early cited studies) remains to be investigated systematically.

Long-term metabolic studies provide a more valuable index of adequacy of intake than do short-term studies. Figure 1-5 shows that on very low intakes (< 4 mg/kg/day) the young men remained in negative balance for the average of 52 days of study, whereas the young women retained sufficient magnesium at the end of

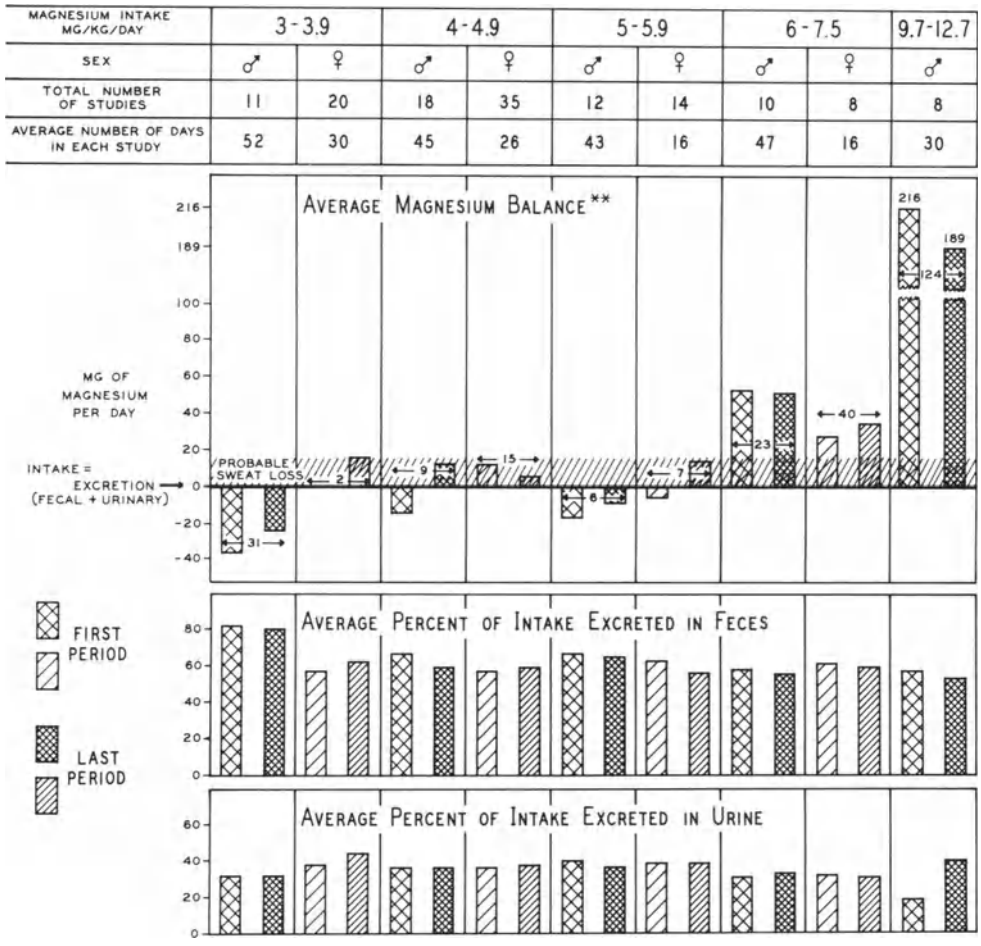

FIGURE 1-5. Comparison of first and last balance periods on long-term magnesium balance studies of men and women. *12–126 days. **Horizontal arrows indicate weighted average over entire period. (From MS Seelig: *Am J Clin Nutr* 14:342–390, 1964.)

their 30 days to maintain equilibrium, even taking into account probable sweat loss. On the usual American intake of 4–4.9 mg/kg/day, the young men went into equilibrium at the end of the study; the young women were in magnesium balance throughout. Why there was less magnesium retention by the young men whose intakes were slightly higher (5–5.9 mg/kg/day) is puzzling. Perhaps that group happened to have higher intakes of nutrients that interfere with magnesium absorption or increased renal magnesium excretion. Continuation of strong positive balances after a month on supplements that raised the magnesium intakes of young men to 9.7–12.7 mg/kg/day suggests restoration of a deficit. A subsequent study by Irwin and Feeley (1967) showed sustained strongly negative magnesium balances (−77, −74, and −38 mg/day) in 15 healthy women evaluated for 3 consecutive 20-day periods that delivered 230–300 mg of magnesium daily. They concluded that the recommended daily intake of magnesium (300 mg) is insufficient to maintain magnesium

equilibrium in 140-lb women, and suggested that the proposed intake of 385 mg/day (Seelig, 1964) might be a preferable amount. In a long-term study (50 and 20 weeks) of 3 men on magnesium intakes of 1.8 mg/kg/day to 5 mg/kg/day, Tipton and Stuart (1970) found that the young man who weighed 100 kg who was on the diet delivering the least magnesium (180 mg/day) or 1.8 mg/kg/day lost an average of 90 mg of magnesium daily during the 50-week study. A smaller (71 kg) young man given twice as much magnesium (that provided 5 mg/kg/day) retained an average of 70 mg/kg/day. An 85-kg middle-aged man who was fed a diet containing 310 mg of magnesium daily (3.8 mg/kg/day) lost an average of 40 mg daily during the 20 weeks on study. In a long-term study of men (in a Veterans Administration Hospital Metabolic Unit) Spencer *et al.* (1976/1980) found that increasing the magnesium intake about fourfold over the amount supplied (about 250 mg) in the basic diet did not consistently increase the amount of magnesium retained. About two-thirds of the supplement was excreted in the feces. The amount of calcium and phosphorus in the diet and the duration of the metabolic periods influenced the results. On low to high daily calcium intakes, magnesium-supplemented (about 500 mg/day patients retained about 49 to 58 mg of magnesium daily on low calcium intakes (200 mg daily). Patients on 1400-mg calcium intakes remained in slightly negative magnesium balance (−8 mg/day) when they were supplemented with magnesium; when they were not given the extra magnesium their daily magnesium loss was 20 mg. Adding the magnesium supplement to a diet plus calcium supplements providing 2000 mg of calcium raised the magnesium balance from +2 to +85 mg/day. Increasing the phosphorus intake to close to 1500 mg from 975, converted a positive magnesium balance (+29) to a negative one (−19 mg/day) during a period of low calcium intake, but not when the calcium intake was also increased. Spencer *et al.* (1979) suggested that the different amounts of magnesium retained by the different supplemented patients might have reflected their prior magnesium status. This impression is supported by the high retentions of magnesium by supplemented subjects who had previously been subjected to magnesium deprivation (Fitzgerald and Fourman, 1956; Shils, 1964, 1969a,b). They (Spencer *et al.* 1976/1980) also stressed the importance of the duration of the study, noting that, during the early phase of their studies, the positive magnesium balances were strong; several weeks later, the patients were in equilibrium or even in slightly negative balance. Perhaps this reflects repletion of an insufficiency, such as had been postulated might occur with sufficiently sustained magnesium supplementation (Seelig, 1964).

The cited dietary surveys and metabolic balance studies support the contention that magnesium supplied by the American diet—and most likely by that of most industrialized countries, particularly those populated by Europeans or by those with comparable eating habits—is likely not to be optimal. Such intakes, which are at best marginal, can be frankly deficient when there are concomitant high intakes of nutrients that increase magnesium requirements. Manifestly, although the incidence of abnormalities that resemble those produced in experimental or conditioned magnesium deficiency has increased during the years that the dietary pattern has changed to one that leads to at least conditioned magnesium deficiency, such abnormalities are not found in the entire population. Individual (or familial or group) differences in dietary habits can be partially responsible. (Table 1-4 gives magnesium content of foods.) Also probably contributory are genetic differences in utili-

TABLE 1-4. Magnesium Content of Foods (mg/100 ml)

Foods rich in magnesium (over 100 mg/100 ml)	
Cocoa and chocolate	
Cocoa	420[a],192[b]
Bitter chocolate	292
Sweet chocolate	107–131[a]
(Milk chocolate	59)
Nuts	
Cashew	267
Almonds	255
Brazil nuts	225[a]–411[b]
Barcelona nuts	202
Peanuts	167[a]–181[b]
Pecans	151[a]
Hazel nuts	140[a]
Walnuts	132
Seafood	
Winkles, boiled in fresh H_2O	414
Conch	246
Shrimp	79[a],105[b]
Whelks	160
Vegetables	
Soybeans	255[a]
Butter beans	164[b]
Soya flour	235–286[b]
Dried beans	159–181[a]
Dried peas, raw	116–140[a]
Beet greens	113
Grain	
All bran	420[b]
Whole barley	171[a]
Whole rye flour	155[a]
Whole wheat flour	147[a]
Oats, raw	113[b]–145[a]
Maize	120[a]
Brown rice	106[a]
Foods with 50–100 mg/100 ml magnesium	
Seafood	
Clams	89
Cockles	51
Crabs, boiled	50
Grain and grain products	
Corn meal	86[a]
Whole wheat bread	60[b]–74[a]
Rye flour	65[a]
Nuts and dried fruit	
Dried figs, raw	82[a]–92[b]
Dried coconut	77[a]–90[b]
Dried apricots, raw	65
Dates	59[b]–65[a]
Cob nuts	56
Fresh coconut	52[b]
Vegetables	
Collards	55
Spinach, boiled	52[a]–59[b]
Chard	53
Foods with moderate content of magnesium (25–50 mg/100 ml)	
Seafood and fish	
Boiled lobster	34
Prawns	42
Oysters	39[a]–42[b]
Canned sardines	41
Smoked sprats	40
Mackerel	33
Bluefish	31
Salmon	29
Fried whitebait	50
Herring	26[a]–35[b]
Haddock	26 –28
Steamed flounder	25
Grain and grain products	
Macaroni, raw	57
Corn meal	38[a]
White flour	37
Pearled barley	20[b]–37[a]
White rice	28[a]
Nuts and fruits	
Chestnuts	33[b]–42[a]
Fresh coconut	39[a]
Dried peaches	54
Dried prunes	44
Avocado	41
Bananas	31[a]–42[b]
Dried currants	30[b]
Raisins	27[a]–42[b]
Blackberries, raw	22[a]–29[b]
Vegetables	
Parsley	41
Sweet corn	38
Okra	38
Kale	37
Kohlrabi	37
Horseradish	36
Dandelion	36
Green cabbage	34
Fresh peas	33
Parsnips	29
(Brussels sprouts	28[a])
String beans	27
Globe artichokes, boiled	27
Celery	25
Fresh peas, raw	30
Dried peas, boiled	30
Potatoes, baked in skin	29

(*continued*)

TABLE 1-4 (*Continued*)

Dairy products	
Hard cheese	42[a]–47[b]
Meat[b]	
Fried liver	24–27
Roast heart	35
Bacon, fried	25–32
Corned beef	29
Roast beef, lean only	25
Grilled steak	25
Veal-fried, roast	28–33
Foods relatively poor in magnesium (under 25 mg/100 ml)	
Meat and fish	
Roast pork lean	24
Grilled lamb	24
Veal	23
Boiled beef	20[b]
Boiled tongue	13
Boiled ham	17–24
Roast beef, lean and fat	19
Kidney	16
Brain	13–17
Halibut	24
Steamed cod	20
Cooked chicken, duck, & turkey	17–23
Fried cod	24
Fruit	
Raspberries	22
Blackberries	22
Fresh figs	21
Cantaloupe	17[a]–20[b]
Fresh currants	13–17
Cherries	14
Strawberries	12
Plums, peaches	10–11
Oranges	11[a]–13[b]
Pineapple, fresh	11[a]–17[b]
Pineapple, canned	8
Grapefruit	10
Fresh apricots, Apples, Pears, Cranberries, Grapes	Below 10
Vegetables	
Fresh peas, boiled	21
Potatoes, boiled	24
Broccoli, boiled	14
Beets	23
Cauliflower, boiled	7
Cabbage, raw	17
Turnips and greens	18
Carrots, raw	12
Mushrooms	16
Onions	7[a]–16[b]
Eggplant	15
Radishes	15
Lettuce, endive	10–12
Lentils, boiled	21
Tomatoes	12
Asparagus, boiled	5
Cucumber	9
Carrots, cooked	6–8
Brussels sprouts, boiled	11[b]
Cabbage, boiled	7
Dairy Products	
Eggs	13
Milk	13–14
Cream	12
Butter	1
Grain	
Oatmeal porridge	13
White rice, raw	13[b]
White rice, boiled	4[b]
Macaroni, boiled	17[b]

[a] Values based on data from HC Sherman (1945).
[b] Values based on data from RA McCance and EM Widdowson (1960).

zation or retention of magnesium and in vitamin D metabolism (Seelig, 1969b, 1970a,b). It is hoped that future investigation will resolve whether the familial instances of parathyroid dysfunction and of some congenital cardiovascular or renal diseases are related to basic genetic variants in the handling of magnesium and vitamin D, and whether those two recognized genetic variants are interrelated.

One wonders whether the demonstrated better retention of magnesium by women than men on marginal magnesium intakes can contribute to the dramatic sex difference in incidence of IHD in young adults (Table 1-5; Figure 1-1) and to the rise of incidence in death rates in Canada from 1926 to 1961 (Fig. 1-6, T. Anderson, 1973). The sharp increase that occurred only in middle-aged men was entirely in the

TABLE 1-5. Sex and Age Differences in Mortality Rates from Arteriosclerotic Heart Disease (per 100,000 White Population)[a]

Age	Men	Women	Sex difference, men/women
25–29	4.3	1.0	4.3:1
30–34	15.8	2.7	5.9:1
35–39	50.1	6.5	7.7:1
40–44	124.2	19.4	6.4:1
45–49	254.9	40.8	6.2:1
50–54	462.6	85.6	5.4:1
55–59	719.0	183.6	3.9;1
60–64	1,119.1	384.4	2.9:1
65–69	1,622.0	687.5	2.4:1
70–74	2,291.1	1,211.0	1.9:1
75–79	3,243.2	2,053.9	1.5:1
80–84	4,802.5	3,508.1	1.3:1
>84	7,248.7	6,233.7	1.2:1

[a] Adapted from J S Stamler (1963).

IHD category; cardiac death rates from other causes dropped. Among the women, the cardiac death rate remained the same, but the proportion due to IHD rose. There was a lesser sex difference in the proportion of deaths that occurred suddenly in the middle-aged groups in hard- and soft-water cities in Ontario, and still less in the 65 to 74 year-old groups (T. Anderson *et al.* 1976/1980). Whether the observation of this group that myocardial magnesium levels were lower in women who had

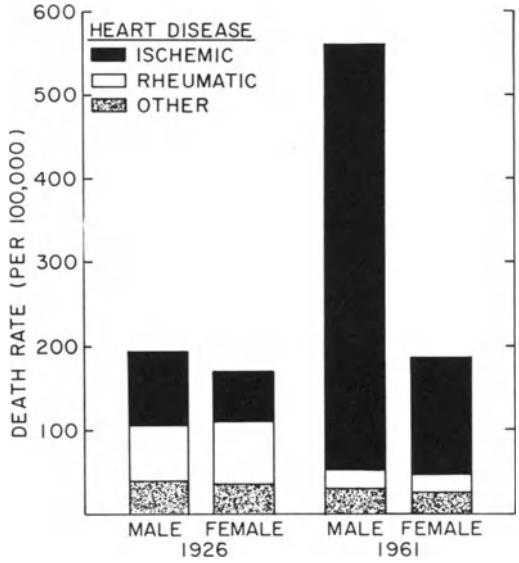

FIGURE 1-6. Male and female death rates from heart disease in Canada in 1926 and 1961 in the age group 45 to 64. (From T Anderson, 1973.)

died suddenly (accident or suicide) than they were in comparable men, both in hard- and soft-water areas (T. Anderson *et al.*, 1978), bears on this question requires resolution. On the surface it would seem to militate against the concept that women's better retention of magnesium explains the sex difference in the rise of IHD. Additional factors must be considered. Among such factors are those diagrammed by Raab (1972), who had earlier provided experimental evidence that stress causes decreased myocardial magnesium levels (Raab *et al.* 1968). Does this imply that women are more subject to stress-induced decreased myocardial magnesium? This seems dubious. More likely, women normally have less myocardial magnesium than do men. Does the amount of muscular exertion play a role? The higher myocardial magnesium levels in left than in right ventricles (Holtmeier, 1969a; Szelenyi, 1973) might be germane to this point.

The evidence that dietary magnesium is generally insufficient and that under those conditions women retain more than do men, is clear, however—wherever the magnesium goes. It provides some insight into the provocative epidemiologic studies that demonstrate that the cardiovascular death rates are higher in areas supplied with soft water than they are in hard water areas. N. Goldsmith (1969) and Hankin *et al.* (1970) have calculated that 12% of the daily intake of magnesium can be derived from water. Among those using only hard water, as much as 18% of the daily magnesium intake may derive from water. Among those whose magnesium intakes from food are marginal, these amounts might well be critical.

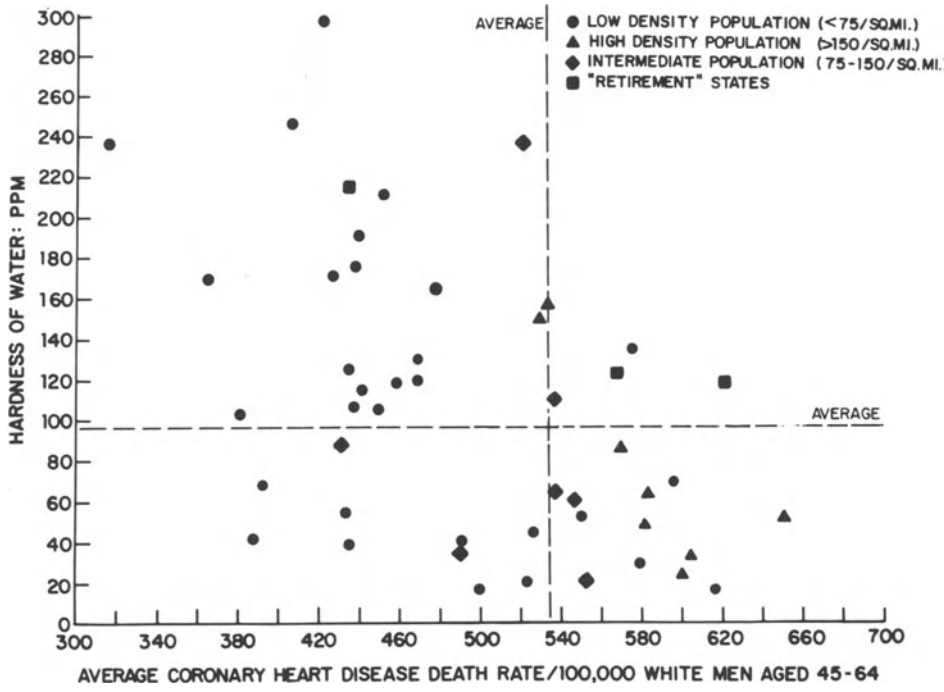

FIGURE 1-7. Correlation of coronary heart disease death rates (1950) with hardness of water by states in U.S.A. (white men, aged 45–64). (Adapted from Schroeder, 1966: from MS Seelig and HA Heggtveit: *Am J Clin Nutr* 27:59–79, 1974.)

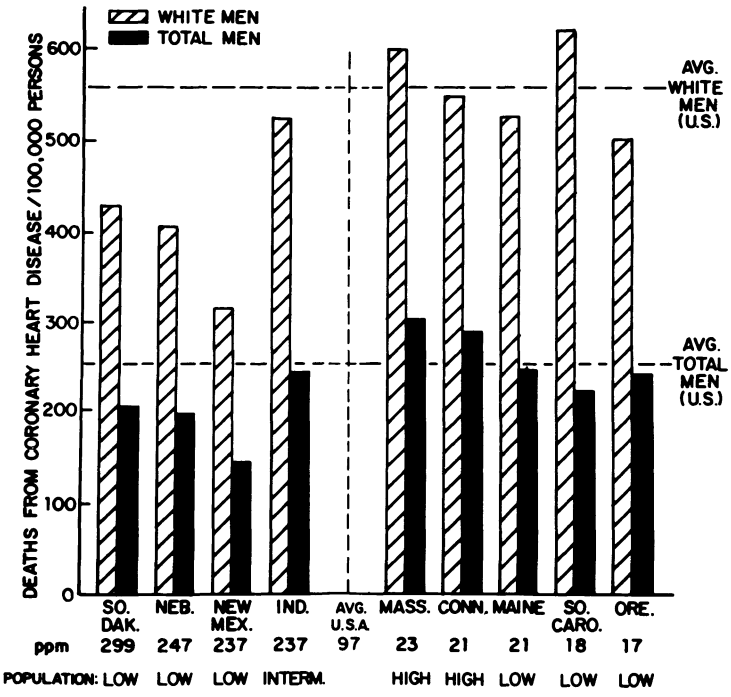

FIGURE 1-8. Deaths from ischemic heart disease: white men (aged 45–64 years) versus total population men* by states with hard versus soft water. *Age corrected. (Adapted from Schroeder, 1966: from MS Seelig and HA Heggtveit: *Am J Clin Nutr* 27:59–79, 1974.)

1.5. Hard/Soft Water and Cardiovascular Disease

J. Kobayashi (1957) first noted that the nature of drinking water might influence death rates from cardiovascular disease; the incidence of strokes is high in areas with acid (soft) water. Schroeder (1960a,b, 1966) surveyed the hardness of drinking water in each of the United States, and correlated the death rates with state-wide water hardness or softness (Fig. 1-7). He found that death rates from cardiovascular diseases (particularly from "coronary" heart attacks in white men 45–64 years old) were significantly higher in states with soft water than in states with hard water (Fig. 1-8). The death rate in South Carolina, a state with the softest water, was 983/100,000; that in Nebraska, a hard-water state, was 712/100,000. Deaths from cerebrovascular accidents followed a similar pattern. Complicating interpretation of these findings is the fact that ischemic heart disease death rates are higher in urban than in rural communities. To eliminate this factor, the coronary death rates from three cities with hard-, intermediate-, and soft-water supplies are compared (Fig. 1-9), and reveal a startling contrast between the rates of fatal ischemic heart disease in cities with hard and soft water. Since this observation, there have been many confirmatory studies, although there has not been complete accord that it is the magnesium, rather than the calcium, that is protective, or whether there might be a toxic element in the soft water that is to blame, e.g., cadmium (Perry, 1973), copper

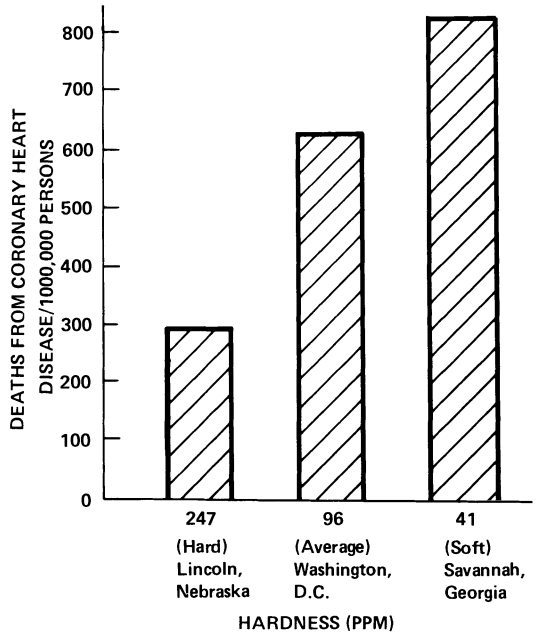

FIGURE 1-9. Deaths from ischemic heart disease: white men (aged 45–64 years) in cities with hardest, average, and softest water, (from MS Seelig and HA Heggtveit: *Am J Clin Nutr* 27:59–79, 1974.)

(Harman, 1975/1977), or others (Editorial, *Lancet,* 1969c).On the other hand, Klevay (1975, 1977, 1978) has presented provocative evidence that a high zinc/copper dietary ratio might contribute to ischemic heart disease as a result of relative copper deficiency, which causes a decrease in high-density lipids and an increase in low-density lipids. He has suggested that hard water might be protective by lowering the ratio of zinc to copper. Where hard water is artificially softened (i.e., by sodium chelates), the role of increased sodium should also be considered.

M. Crawford *et al.* (1968) like others working in areas where calcium is by far the major water factor (J. Morris *et al.,* 1962; Biorck *et al.,* 1965; J. Robertson, 1968, 1969), favored calcium as the probable protective factor. In England, the average calcium content of hard water accounts for about 84% of the hardness and is more than 11 times greater than the magnesium content (M. Crawford *et al.* 1968). Nonetheless, it was her impression that the water-protective "factor" probably involves interrelationships of the "bulk" ions: calcium, magnesium, and sodium (M. Crawford, 1972). Those who had had favorable experience with the use of magnesium salts in treating patients with acute or chronic IHD (R. Parsons *et al.,* 1961; Berberian, 1962; Browne, 1961, 1963, 1964a,b) favored magnesium as the hard-water protective factor. So also did those who had done or evaluated animal work that showed magnesium to be protective and excess calcium either not protective or harmful in experimental cardiomyopathies or soft-tissue calcification (e.g., cardiovascular and renal) (Neal and Neal, 1962; Marier, 1963; Bajusz, 1967; Marier *et al.,* 1968; Seelig and Bunce, 1972; Seelig and Heggtveit, 1974). In his

consideration of the part played by hard water, Bajusz (1967) suggested that the higher content of magnesium might protect the myocardial cell against damage caused by ischemia and improve its ability to resist the effects of cardiotoxic agents. In 1974, Seelig and Heggtveit considered the experimental and clinical evidence that calcium and magnesium exert reciprocal effects on myocardial irritability. High calcium levels stimulate and high magnesium levels suppress hyperexcitability. They then suggested that magnesium might be useful in maintaining normal cardiac rhythmicity, in the face of ischemia or digitalis-toxicity, or in acute (i.e., alcohol- or diuretic-induced) hypomagnesemia. [The antiarrhythmic attribute of magnesium is again being utilized in the United States (Chadda *et al.*, 1973a,b, 1976/1980; Iseri *et al.*, 1975; Iseri and Bures, 1976/1980) after a hiatus of 30 years (Boyd and Scherf, 1943).]

The dietary surveys presented here show that magnesium, but not calcium, intakes have been gradually falling. Coinciding in time with the sharp increase, first of vitamin D and then of phosphorus intakes (Fig. 1-1), there has been a steep increase in incidence of sudden deaths from IHD (T. Anderson and LeRiche, 1970). The recognition of this increase in IHD death rates derived from an extensive study of death certificates of men 45–64 years of age (Ontario, 1901–1961). As many as 5000 certificates a year had to be examined when the incidence was low (in 1901). Where deaths from IHD were clearly specified, as compared with all cardiac deaths, it was the IHD category that had risen, more than doubling from 1931 to 1961 (Anderson and LeRiche, 1970). The death rates from other major forms of heart disease in that age group had fallen during the same period of time. The minor changes in cardiac death rates from 1901 to 1931 are not as readily interpreted, because of changes in terminology and possible incompleteness of reporting. Selecting 1931 as the earliest key date (sudden-death coroner reports being available from about 1931 on Toronto), these investigators found that only about half of the nontraumatic sudden deaths were attributed to IHD in 1931, whereas 99% were deemed due to IHD in 1961. Spain *et al.* (1960), on the basis of an autopsy survey, considered such events the commonest cause of death of middle-aged men, at about the same time. T. Anderson *et al.* (1969) postulated that there might be an environmental factor that could, by altering myocardioal excitability, cause an increase in the incidence of sudden death from ventricular fibrillation and other cardiac arrhythmias, and noted that the sudden death rate (but not the nonsudden IHD death rate) varies inversely with the hardness of the water. T. Crawford and M. D. Crawford (1967), who had noted that despite a much higher frequency of cardiac death rates in Glasgow (a soft-water area) than in London (a hard-water area) degrees of coronary atherosclerosis were not dissimilar, had also suggested that the water factor might affect the way the myocardium reacts to ischemia. They found that the coronary magnesium content was higher in young men (under 40) who had died as a result of accidents in London than in Glasgow, and that the Scottish young men had more small myocardial scars than did the Londoners.

From Ontario, where the magnesium content of hard water is much higher than it is in England, has come much of the definitive data implicating magnesium rather than calcium as the protective factor in hard water, and ruling out most of the potentially toxic trace minerals found in soft water as the harmful soft-water factor.

In their surveys of cardiac death rates, T. Anderson *et al.* (1969) found that there were many more (sudden) cardiac deaths reported in soft- than in hard-water areas (T. Anderson *et al.*, 1978). This supported T. Crawford and M. D. Crawford's (1967) and Bajusz's (1967) suggestion that the hard-water factor was likely to be a myocardial protective factor. They speculated that it probably affected cardiac rhythmicity (T. Anderson *et al.*, 1969, 1973, 1976/1979; T. Anderson and LeRiche, 1970, 1971). Comparable findings were reported by Fodor *et al.* (1973) from Newfoundland, where there is a much higher death rate for IHD in a city with very soft water than in two communities with hard water, particularly for men, 62% of whom died before they could be brought to the hospital (considered probable sudden deaths). They commented that IHD death rate in men in the soft-water city (702/100,000) is comparable to that in the "high mortality belt" of the southeastern portion of the United States.

At first Anderson *et al.* (1969) adhered to the English premise that calcium was likely to be the protective water factor. When they became aware of the evidence that Western diets provided marginal amounts of magnesium (Seelig, 1964) and that persons dying of heart attacks have low myocardial magnesium levels, even in non-infarcted segments (Heggtveit *et al.*, 1969; Seelig, 1972), they had pathologists from hard- and soft-water areas secure myocardial specimens from routine autopsies, and had them analyzed for magnesium, calcium, and trace elements (T. Anderson *et al.*, 1973, 1975, 1976/1980). Magnesium was the only element with a significant difference in myocardial concentration, which was higher in hearts of accident victims from hard-water areas (982/918 μg/g dry tissue). IHD disease victims had 22% lower myocardial magnesium levels in soft- than in hard-water areas (697/744). In England, there has been an apparently contradictory pattern (Chipperfield *et al.*, 1976a), with lower levels of myocardial magnesium in hard- than in soft-water cities. T. Anderson *et al.* (1978) point out that since in the two English cities that were compared the magnesium levels are quite low both in the hard and in the soft water (Chipperfield *et al.*, 1976b), the difference between them represents only 1% or 2% of the probable total intake, and that another factor might be operative.

In Finland, which has a very high death rate from IHD, there is a clear relationship with the amount of magnesium in the soil (Karppanen and Neuvonen, 1973). In eastern and in northern Finland, where the soil content is about a third that found in southwestern Finland (Karppanen *et al.*, 1978) the mortality from ischemic heart disease is twice as high as is that in the southwest. Holtmeier and Khun (1976/1980) surveyed factors that might be contributory both to the rising incidence of cardiovascular disease in Europe, and the falling levels of magnesium both in the soil and in the food supply. They commented that in Finland, which has the highest cardiovascular death rate in Europe, the dietary supply of magnesium had decreased by 1963 to a third of the intake common in 1911 (H. Katz, 1973). In contrast, in Japan with its low cardiac death rate, the daily magnesium intake was cited as 560 mg (Holtmeier, 1969a, 1973). Karppanen *et al.* (1978) have depicted the steep rise in ischemic heart disease that coincides with increasing dietary calcium/magnesium ratios (Fig. 1-10).

In view of the possibility that sudden deaths of infants might similarly be mediated by magnesium deficiency, and be analagous to the adult cardiac

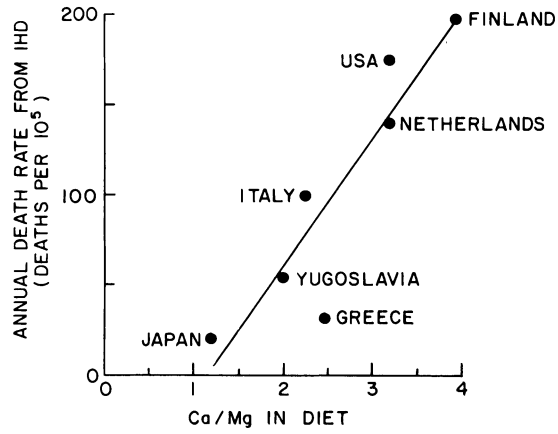

FIGURE 1-10. Ischemic heart disease rates correlated with dietary calcium/magnesium ratios. [From H Karppanen *et al.: Advances in Cardiology*. V Manninen and PI Halonen (Eds), S Karger, Basel, 1978, pp 9–24.]

arrhythmic sudden deaths that are prevalent in soft-water areas, the preliminary report by Godwin and Brown (1973) of a somewhat higher incidence of sudden infant deaths in soft-water counties in California than in hard-water counties is provocative. It must be noted that the following year a conflicting report was published (Allwright *et al.*, 1974) that failed to confirm the higher incidence of either IHD of adults or of infant mortality rates with soft water. However, these investigators point out that this "soft" water is approximately as hard as is the "hard" water in some of the English studies, where higher infant-death rates were reported in soft- than in hard-water areas (M. Crawford *et al.*, 1972). These tentative findings call to mind the instance of sudden infant death that was associated with coronary arteriosclerosis (Meurman *et al.*, 1965) from eastern Finland, and the report by Pesonen *et al.* (1975) on more severe and more frequent infantile coronary arteriosclerosis in eastern Finnish children than in those from the southwest (where the magnesium level is higher).

1.6. Epidemiologic Factors in Calcific Urinary Calculi

There has been an increase, during this century, in the incidence of calcium oxalate stones in Finland (Sallinen, 1960), central Europe and Sweden (Grossman, 1938; Hedenberg, 1951) and Japan (Inada *et al.*, 1958; Editorial, *Brit Med J*, 1965) that coincides with the rising incidence of cardiovascular diseases in those countries, and with the use of magnesium-poor soil fertilizers in the northern and central parts of the European continent (Holtmeier and Kuhn, 1976/1980). The geographic difference in frequency of calcific urolithiasis in the United States (Landes, 1975/1977; Finlayson, 1974; Landes *et al.*, 1977) coincides with the geographic difference in incidence of sudden death from ischemic heart disease, and with the degree of water hardness. A map of the United States, indicating the distribution of water

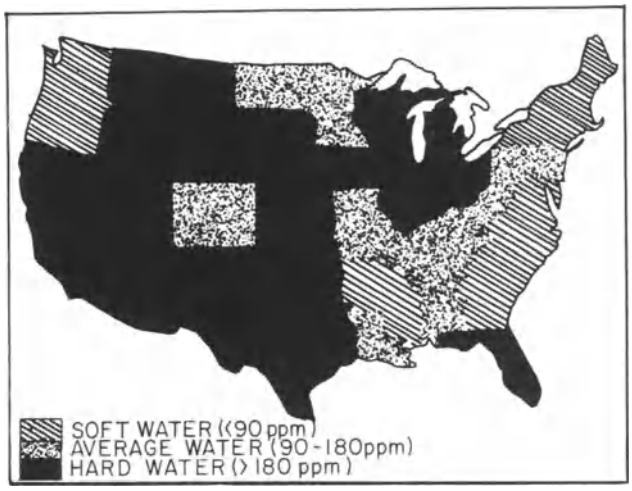

FIGURE 1-11. Distribution of water hardness in the United States in 1963. (From Landes *et al.*, 1975/1977.)

hardness in 1963 (Fig. 1-11) and one showing the incidence of urinary calculi (Fig. 1-12) clearly shows that in most states where the water is softest the frequency of urolithiasis is highest. Boyce *et al.* (1956), who pointed out this geographic overlap, reported that the highest incidences of kidney stones were in South Carolina and other southeastern states, an area that has been called "the kidney stone belt," and the lowest incidences were in midwest and southwestern states, where the water is hard. Melnick *et al.* (1971, 1973) and Landes *et al.* (1977) reaffirmed this observation, basing their conclusions on hospital diagnoses, obtained from a survey done in 1972. South Carolina again came in first, with the highest frequency (17/1000 discharges). Nebraska, the state shown earlier to have the lowest incidence of sudden death from ischemic heart disease, also had the lowest frequency of urinary calculi (2.6/1000 hospital discharges). Accepting the limitations of such state-wide surveys of stone incidence and water quality, the authors nonetheless felt justified in concluding that the differences were statistically significant, indicating that the incidence of urinary calculi is inversely related to the hardness of the water (Landes *et al.*, 1977).

Prien (1971), who had reported that magnesium therapy in conjunction with pyridoxine (Prien, 1965; Gershoff and Prien, 1967), was useful as prophylactic therapy for recurrent calcium oxalate stone-formers (in northern New England, another soft-water area), presents "the riddle of urinary stone disease." He referred to Grossmann's (1938) evidence that, starting in 1924, the incidence of small calcific stones in young adults rose in central and northern Europe, and was puzzled as to why the incidence should have dropped during World War II, only to rise again thereafter (Boshamer, 1961). It is possible that the work of Linden (1972, 1974a, 1977) correlating concurrent urolithiasis, hyperlipidemia, and ischemic heart disease with only moderately high intakes of vitamin D might be germane to the rise in incidence of kidney stones after 1924. Linden (1977) mentioned that after Mellanby

(1920) had demonstrated that cod liver oil could prevent rickets, it was soon widely used for lesser ailments, such as failure to thrive and poor appetite. He referred to reports, in the late 1920s, of infantile fatalities due to hypervitaminosis D. It is possible that inappropriate and widespread use of vitamin D, which increases magnesium requirements, might have intensified magnesium deficiency, the predisposition for which might have derived from the decreased magnesium-availability from the soil, especially in those parts of central Europe where fertilizers high in potassium and low in magnesium were commonly used after World War I (Aleksandrowicz and Stachura, 1976/1980; Holtmeier and Kuhn, 1976/1980). Perhaps, during World War II, the vitamin D supplements and soil fertilization were less widely used, only to be taken up again after the war. In the last year of World War II, and for more than a decade thereafter, in the British Isles, excessive vitamin D was provided in infant formulas and other foods, with a resultant epidemic of supravalvular aortic stenosis syndrome (SASS) and increased incidences of renal tubular acidosis, infantile nephrocalcinosis, and osteosclerosis. In Germany, "Stosstherapie" with huge parenteral doses of vitamin D also caused SASS and related "congenital" abnormalities (Review: Seelig, 1969b). To what extent the long-term use of therapeutic doses of vitamin D in infants and children with low requirements or hyperreactivity to vitamin D (Seelig, 1970a,b), and to what extent its continued use throughout life, and especially during adolescence and early adulthood when milk consumption tends to be high (in America), might predispose to a high urinary calcium/magnesium ratio and to a conditioned magnesium deficiency should be systematically investigated. Possibly it might be part of the answer to Prien's kidney-stone riddle (1971), as well as to the continued high sudden-cardiac death rate.

The inverse relationship between the tendency toward calcium oxalate urinary tract stones and the tendency toward osteoporosis (McGeown and Oreopolis, 1969)

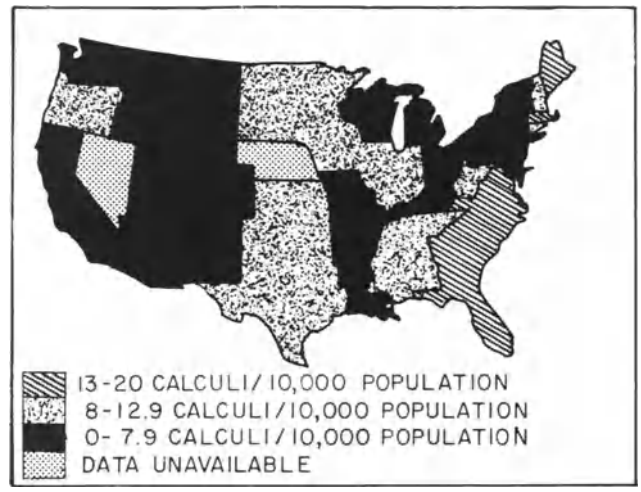

FIGURE 1-12. Incidence of urinary calculi requiring hospitalization in 1952. (From Boyce *et al.*, 1956, and Landes *et al.*, 1977.)

is provocative. There are fragmentary data indicating that magnesium deficiency contributes to several pediatric osteopenias and to osteoporosis, all of which are characterized by loss of matrix. A high Ca/Mg ratio might favor hypermineralization of bone with defective matrix. High P/Ca and P/Mg ratios might favor osteomalacia. Correlation of these mineral ratios with hormonal responses might shed some light on the high rate of osteoporosis in postmenopausal women, who might have a high parathyroid/estrogen ratio, in addition to loss of the estrogen-induced capacity to store magnesium in bone. Whether low magnesium and high vitamin D intakes during pregnancy contribute to osteogenesis imperfecta, hypophosphatasia, and fragile bones of low-birth-weight infants should be studied.

1.7. Genetic Factors in Cardiovascular, Skeletal, and Renal Diseases

Even though the dietary factors (high vitamin D and phosphate intakes and declining magnesium intakes) have been widespread, and in the case of vitamin D unavoidable for milk-drinkers, the increased incidence of frequency of some cardiovascular, skeletal, and renal diseases has not been distributed equally in the population. Except for osteoporosis, which is most prevalent in white postmenopausal women (McGeown, 1969; Meema *et al.*, 1973, 1975; N. Goldsmith and Johnston, 1978), and hypertension, which is most prevalent in black women (Kuller *et al.*, 1973), most of the diseases for which evidence is presented in this volume, of relationships to low magnesium, to vitamin D, and to phosphate intake, are most prevalent in white males. Furthermore, there is evidence of familial predisposition to what may be risk factors: (1) specific magnesium malabsorption and renal wasting, and (2) hyperreactivity to vitamin D (Seelig, 1969b, 1970a,b). It is suggested that the familial instances of calcium oxalate urolithiasis (McGeown, 1960; Resnick *et al.*, 1968), of pseudohypoparathyroidism with vitamin-D-resistant rickets (DeLuca *et al.*, 1967; Falls *et al.*, 1968; Reitz and Weinstein, 1973), and possibly of hyperparathyroidism (Cutler *et al.*, 1964; Cholod *et al.*, 1970; Marx *et al.*, 1973) might also be secondary to a primary abnormality in magnesium metabolism, leading to magnesium deficiency. Several forms of neonatal or infantile cardiovascular disease, possibly including juvenile hyperlipidemia and hypertension, might also be related to abnormalities in magnesium or vitamin D metabolism, or both, as might vitamin-D-resistant rickets. The familial instances of these diseases and of other osteopenias, which are not infrequently associated with renal disease, might have an underlying defect: magnesium malabsorption or renal tubular wastage or both.

The renal and skeletal disorders contribute to significant morbidity. The cardiovascular complications lead both to morbidity and sudden mortality. An editorial (*JAMA*, 1972) entitled "A Magic Carpet Is Not Enough" calls urgent attention to the fact that as many as over 50% to 73% of sudden deaths from lethal arrhythmias (Kuller *et al.*, 1967; Armstrong *et al.*, 1972) occur before the patients reach the hospital. Among almost a thousand cases of medically untreated deaths from IHD in which autopsies were done, 60% of the men and 47% of the women died within 15 minutes of onset of symptoms (Wikland, 1971). The reference to the inadequacy

of the "magic carpet" pertained to the finding that even if the patient is resuscitated, death is usually merely somewhat delayed by a period of invalidism (Geddes *et al.*, 1967). In a confirmatory study, Kuller *et al.* (1973) showed that 75% of those who died suddenly had had no serious disability; only 12% had been unable to work. Among those who died in a hospital, only 17% survived more than 24 hours. Of the almost 500 who died within 24 hours of onset of symptoms who were autopsied, only 13% had evidence of a recent infarct. The investigators concluded that their findings indicated that no current community health approach will be effective.

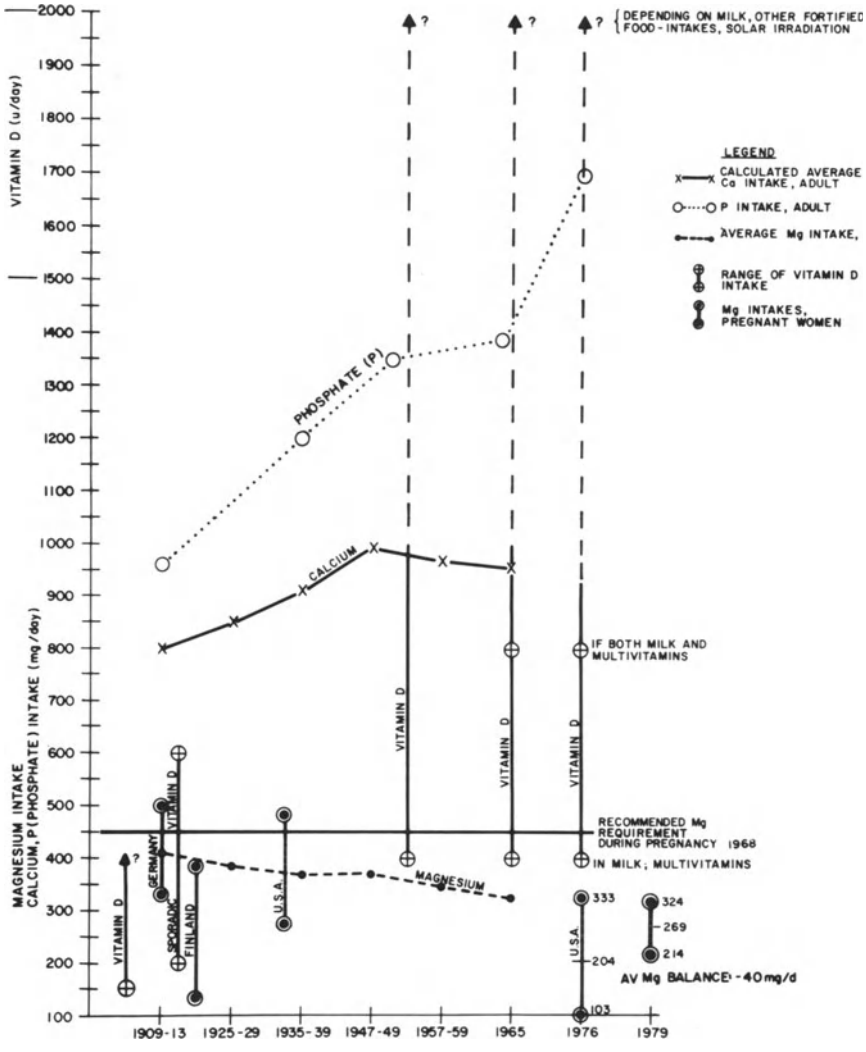

FIGURE 1-13. Magnesium intakes during pregnancy: changing average intakes of magnesium, calcium, vitamin D, and phosphorus during the 20th century. (Derived from Friend, 1967; Seelig, 1969b, 1978, 1976/1980; Johnson and Philipps, 1976/1980; and Ashe *et al.*, 1979.)

They state that a fundamental change in therapeutic and preventive approach is needed.

The correlation of data implicating interrelationships between absolute magnesium deficiency and the magnesium-losing excesses of vitamin D and phosphates in so many of the diseases that have increased in incidence during the time that these dietary imbalances developed might point toward the new approach that Kuller *et al.* (1973) said was required. Such imbalances are a particular risk during pregnancy (Fig. 1-13). Possibly they might lead to abnormal pregnancy, to congential abnormalities, and to infantile and later morbidity and mortality.

Now that vitamin D has been proved to have a steroid hormone mode of action (Norman, 1968; Norman *et al.*, 1975/1977; DeLuca, 1969, 1976), and the active antirachitic metabolites have been isolated, synthesized, and made available, vitamin-D-resistant rickets can be treated specifically, in preference to putting an entire population at risk of hypervitaminosis D by fortifying milk and other foods (Seelig and Mazlen, 1977). Perhaps the popular soft drinks that provide so much of the excess phosphate can be reformulated to be bubbly by other means than by use of phosphate salts. And, finally, physicians should evaluate their patients, particularly those with the cited familial disorders—for abnormal magnesium metabolism, and they should prescribe supplements when needed.

This volume places major emphasis on the early establishment of cardiovascular, skeletal, and renal lesions—possibly during gestation, infancy, and early childhood—that can either cause early manifestations of disease or death, or lay the groundwork for disease processes that become overt later in life. Thus, the first part deals with prenatal, perinatal, and infantile disorders, and the subsequent parts deal more generally with the abnormalities of the three systems to which magnesium deficiency might well be contributory.

I

MAGNESIUM DEFICIENCY DURING GESTATION, INFANCY, AND EARLY CHILDHOOD

2
The Role of Magnesium in Normal and Abnormal Pregnancy

2.1. Magnesium Balance in Pregnancy

The formation of new tissue (maternal and fetal) during pregnancy requires higher magnesium intakes than that of the normal nonpregnant woman of comparable age. The most recent recommended dietary allowances in the United States and Canada is 450 mg/day (Food and Nutrition Boards, 1968), a figure that is probably based largely on magnesium balance determinations and calculations done with adult pregnant women from 1914–1942. The general statement that the dietary magnesium during pregnancy should substantially exceed the amount required by other adults has led to the selection of 450 mg/day as reasonable, exceeding that recommended for adolescent and young adult women in the United States by 100 mg/day and exceeding the amount recommended in Canada for women over 22 by 150 mg/day. Since adolescent children require much higher magnesium intakes to meet their own growth and maturation needs, it is questionable whether the same amount deemed necessary for the mature pregnant woman is sufficient for a teenaged pregnant girl. Even the amount generally considered sufficient, but rarely met by the American woman, whether or not she is pregnant (Seelig, 1964; N. Johnson and Phillips 1976/1980; Ashe *et al.*, 1979), should be reevaluated.

Examination of magnesium retention by pregnant women on different dietary intakes (Table 2-1, Seelig, 1971) shows marked differences in retentions, ranging from negative to strongly positive. The first detailed metabolic balance studies of pregnant women (in Germany) that gave magnesium, calcium, and phosphorus intakes and retentions (Table 2-2, Landsberg, 1914) showed strongly positive balances of all these elements. The magnesium contents of the self-selected diets of 14 women ranged from 338–512 mg/day, and their calcium and phosphorus intakes were usually between 2 and close to 3 g a day. Hoffstrom's long-term study of a Finnish pregnant woman's metabolic balances during the last 23 weeks of pregnancy (Table 2-3, Hoffstrom, 1916) showed that on her much lower magnesium intakes, she was in negative magnesium balance during nine of the periods and

TABLE 2-1. Magnesium Intakes and Retentions during Pregnancy

Investigator(s)	Number of observations: Women	Number of observations: Metabolic periods	Mg intake range (mean) (mg/day)	Mg retention range (mean) (mg/day)
Hoffstrom (Finland)	1	23	177–395 (282)	−176 to +188 (+13)
Landsberg (Germany)	14	14	338–512 (457)	+2 to +159 (+56)
Toverud (Norway)	16	27	186–688 (341)	−47 to +255 (+99)
Toverud (Norway)	23	30	186–688 (368)	0 to +322 (+132)
Coons-Blunt (Chicago, Illinois, U.S.A.)	9	23	236–810 (375)	−311 to +81 (−85)
Coons (Oklahoma, U.S.A.)	6	23	285–471 (394)	−3 to +154 (+63)
Coons and Coons (Oklahoma, U.S.A.)	1	18	369–561 (455)	−7 to +63 (+18)
Hummel *et al.* (Detroit, Michigan, U.S.A.)	1	28	480–760 (600)	+30 to +230 (+110)
Hummel *et al.* (Detroit, Michigan, U.S.A.)	1	13	350–430 (390)	+10 to +160 (+60)

retained less than 50 mg/day in eight more. Despite her adequate calcium and phosphorus intakes in all but four periods (never falling below 1 daily) she was in negative calcium balance during seven periods. She rarely retained as much calcium or phosphorus as did the women in the German study (Landsberg, 1914).

The emphasis in the United States was largely on the problem of calcium retention, and Coons and Blunt (1930) at first studied magnesium balances of pregnant

TABLE 2-2. Average Magnesium, Calcium, and Phosphorus Intakes and Retention in Pregnant Women on Self-Selected Diets[a]

Lunar month	Magnesium (mg/day): Intake	Magnesium (mg/day): Retention	Calcium (mg/day): Intake	Calcium (mg/day): Retention	Phosphorus (mg/day): Intake	Phosphorus (mg/day): Retention
2	489	+3	2913	+16	2624	+97
	411	+2	2689	+21	2791	+142
3	338	+5	1821	+26	2186	+285
	468	+9	2743	+213	2732	+296
	512	+12	2817	+298	2579	+325
4	478	+28	2935	+312	3010	+501
	425	+39	2489	+356	2914	+492
	463	+35	2763	+348	2581	+535
5	510	+89	2748	+579	2875	+1004
6	472	+102	2915	+742	2469	+1016
7	459	+97	2823	+653	2298	+765
8	423	+107	2474	+781	3102	+1274
9	482	+159	2648	+829	2936	+949
10	475	+101	2597	+748	2847	+893

[a] From data in Landsberg (1914).

TABLE 2-3. Average Magnesium, Calcium, and Phosphorus Balances during the Last 23 Weeks of a Pregnancy[a]

Week of gestation	Magnesium (mg/day)		Calcium (mg/day)		Phosphorus (mg/day)	
	Intake	Retention	Intake	Retention	Intake	Retention
17	361	−40	1892	−330	2060	+72
18	297	−7	1860	+394	2300	+591
19	383	+188	2385	+951	2862	+1005
20	307	−9	2201	−234	2471	+177
21	268	+40	2062	−230	2304	+313
22	295	+5	1921	+378	2223	+482
23	389	+144	1899	+181	2231	+383
24	395	+154	1315	+499	1482	+318
25	224	−151	1748	−143	1927	+222
26	254	−176	1581	+107	1835	+398
27	240	+34	1298	+168	1569	+294
28	211	−34	1193	−55	1458	+68
29	316	+50	1597	+191	1998	+439
30	235	−21	1451	−125	1754	+125
31	276	+23	1908	+295	2136	+391
32	238	+21	1698	+290	1892	+377
33	240	+7	1638	+252	1834	+254
34	263	+51	1786	+501	1909	+490
35	295	+72	1862	+614	1994	+573
36	250	−56	1517	+186	1670	+128
37	286	+54	1884	+406	1957	+388
38	298	+25	1777	+411	1972	+401
39	289	+34	1621	+211	1872	+215
40	177	−70	1031	−19	1149	−150

[a] From data in Hoffstrom (1916).

women to see whether taking milk of magnesia as a laxative would unfavorably influence calcium retention. They found no interference with calcium retention, even on magnesium intakes as high as 810 mg/day. Toward the end of pregnancy, there was a tendency toward more and larger negative magnesium balances, even on daily magnesium intakes of 400 mg/day. They subsequently compared their findings with those obtained by other investigators (Fig. 2-1, Coons, 1935). The composite curve, and the scatter diagrams, show weakly positive and even negative magnesium balances on daily intakes of less than 300 mg/day. In their own study of eight women in Chicago (Coons and Blunt, 1930), half of the metabolic balance periods showed net losses of magnesium. There was a preponderance of positive balances in their Oklahoma studies of six women (Coons *et al.* 1934, 1935); they speculated that the greater exposure to sunlight in Oklahoma might have been responsible for the better magnesium retention in their 1935 studies. To test the possibility that vitamin D was responsible, they studied the effect of cod liver oil on the magnesium retention of a primiparous woman who had also been tested before pregnancy (Coons and Coons, 1935), and whose intakes of magnesium and phosphorus were kept fairly constant. This was a long-term investigation that included 18 metabolic periods of 4 days each on a continuously regulated diet, from the 21st

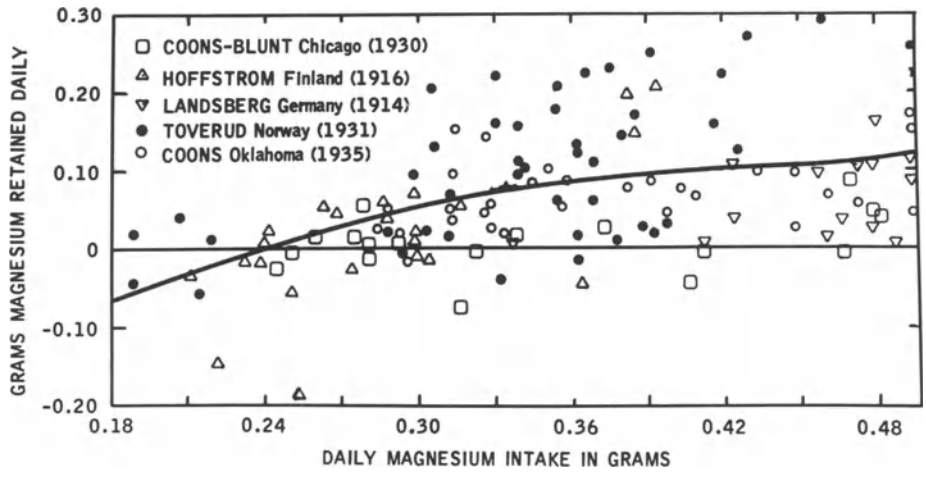

FIGURE 2.1. Compilation of published data on the retention of magnesium during human pregnancy: relation of storage to intake. (From Coons, 1935.)

to 30th weeks of pregnancy. Despite an apparently adequate intake of magnesium (369–561 mg/day), three negative balances occurred during three of the metabolic periods, and the woman's average daily retention of magnesium was only 18 mg. Exposure to sunshine was avoided and cod liver oil supplements were provided only during 25th, 26th, 34th, and 35th weeks of study. The investigators concluded, from the slightly lower calcium and magnesium retentions during the first two weeks of cod liver oil administration at five months gestation, and the minimal changes in calcium retention and slight increase in magnesium retention during the second two weeks of supplementation during the eighth month of gestation, that vitamin D from cod liver oil was not equivalent (in its effects on calcium and magnesium retention) to that from reasonable exposure to sunlight (Coons and Coons, 1935). Table 2-4 includes the above data, and the balance data from the study of Toverud and Toverud (1931), from women whose mineral intakes were kept fairly constant before and while on vitamin D supplementation. The Norwegian study (Toverud and Toverud, 1931) shows that the magnesium balances improved on addition of vitamin D supplements, even when the magnesium intake was low (case 8). In that instance, the vitamin D converted a negative calcium balance on an adequate calcium intake to positive, but did little to correct the negative phosphorus balance, the phosphorus intake also being low. The women whose calcium and magnesium intakes were fairly low, but whose phosphorus intakes were adequate (cases 1,6), responded to vitamin D with more retention of magnesium, much less negative calcium balance in one (case 1) but no significant diminution of the strongly negative calcium balance in the other (case 6), whose phosphorus balances remained strongly positive. Not included in this table are the data from women given diets with and without added calcium as salt and milk, which showed that they required at least 1.6 g of calcium and phosphorus daily to maintain positive balances of those elements. The effects of the increased intake on magnesium retention cannot be determined from that study because the magnesium intake was not constant. In a subsequent study, in which the daily dietary intakes of calcium and phosphorus were kept at 1.5–2 g and

TABLE 2-4. Magnesium, Calcium, and Phosphorus Retentions during Pregnancy as Influenced by Vitamin D Supplements

Investigators	Case	Month of case pregnancy	Form of vitamin D[a–c]	Magnesium (mg/day)				Calcium (mg/day)				Phosphorus (mg/day)			
				No vitamin D		Vitamin D		No vitamin D		Vitamin D		No vitamin D		Vitamin D	
				Intake	Bal.	Intake	Bal.	Intake	Bal.	Intake	Bal.	Intake	Bal.	Intake	Bal.
Coons and Coons															
(1955)	1	5	*a*	441	+28	450	+18	1310	+187	1280	+141	2043	+375	2030	+383
			c				−10				+65				+213
		8	*a*	369	+6	378	+26	1174	+201	1160	+140	1630	+164	1644	+230
							+35				+244				+300
Toverud and															
Toverud (1931)	1	6½–8	*a*	314	+17	314	+68	914	−383	914	−3	1607	+429	1607	+558
							+50				−10				+726
	2	6½–7	*a*	339	+93	339	+102	1162	+145	1162	+360	1451	+401	1451	+411
		8–8½	*c*	344	+76	392	+145	1220	−426	1128	+31	1465	+199	1342	+366
	3	8–9	*b*	304	+20	369	+62	1696	+453	1731	+677	1448	+10	1886	+411
	4	8–9	*b*	381	+13	381	+136	1668	+520	1668	+417	1522	−115	1522	−57
	5	8–8½	*b*	420	+223	336	+157	1451	−231	1431	+71	1432	−248	1540	−101
			b			428	+127			1650	+407			1908	+516
	6	8–8½	*c*	289	+21	289	+49	807	−298	807	−263	1269	+213	1269	+222
	7	8–8½	*c*	362	+133	362	+132	115	+243	1155	+315	1676	+631	1676	+353
	8	8–8½	*c*	186	−42	186	+20	1390	−90	1390	+305	711	−459	711	−345

[a]10 ml cod liver oil (vitamin D_3 + vitamin A).
[b]20 ml cod liver oil (vitamin D_3 + vitamin A).
[c]10 drops vigantol (vitamin D_2).

TABLE 2-5. Magnesium, Calcium, and Phosphorus Retentions during Late Pregnancy[a]

Case	Month of pregnancy	Magnesium (mg/day)		Calcium (mg/day)		Phosphorus (mg/day)	
		Intake	Retention	Intake	Retention	Intake	Retention
1	7	313	+152	1540	+35	1493	+328
2	8½	336	0	1509	+303	1765	+290
3	8¾	331	+322	1711	+764	1966	+1136
4	8	340	+99	1739	+107	1701	+526
5	8	367	+218	1736	+40	1716	+199
6	7½[b]	363	+17	1706	+531	2080	+200
7	8	369	+115	1948	+895	1634	+382
8	8[b]	386	+173	1562	+492	1735	+300
9	8½	392	+253	1625	+638	1843	+901
10	8	380	+31	2032	+598	2151	+675
11	7½[b]	461	+291	1646	+456	1836	+892
12	8	431	+273	1827	+503	1923	+811
13	8	504	+219	2090	+771	2163	+678

[a] From data in Toverud and Toverud (1931).
[b] +10 ml cod liver oil (only in winter months); not all accepted the supplements.

that of magnesium between 313 to 504 mg (Table 2-5), the three women whose magnesium intakes exceeded 430 mg/day all obtained strongly positive magnesium balances. The one with the highest intake, whose intakes of calcium and phosphorus were over 2 g, retained slightly less magnesium than did those with slightly lower calcium and phosphorus intakes. Another woman whose magnesium/calcium/phosphorus intakes were 392/1625/1843 also showed high retentions of all three elements. One with comparable magnesium intake (380) but calcium and phosphorus intakes above 2 g retained only 31 mg of magnesium daily. There are exceptions to these findings; individual differences and variations in intakes of effective elements no doubt influenced the metabolic balances. These data are suggestive that the dietary ratios of magnesium, calcium, and phosphorus, and a requisite amount of vitamin D, all influence the retention of these elements during pregnancy.

The long-term studies of a 37-year-old multiparous woman with a history of three prior successful pregnancies and healthy babies (Table 2-6, Hummel *et al.*, 1936), and of an 18-year-old primipara with a suboptimal nutritional background but on a good diet during pregnancy (Table 2-7, Hummel *et al.*, 1937), provide some data that might be germane to the lower magnesium levels of young primiparas and of their infants at birth. The healthy woman, whose metabolic studies encompassed 28 metabolic balance periods from the 135th to 280th day of pregnancy, was on an unusually rich diet that included two quarts of milk, each of which contained 400 units of vitamin D_3 as cod liver oil. This provided an excess of calcium and phosphorus over that considered desirable, and exceeded that shown by Toverud and Toverud (1931) to decrease the retention of magnesium to +31 mg/day in the woman (case 10, Table 2-5) receiving 380 mg magnesium daily, but not to decrease its retention in the woman (case 13, Table 2-5) who ingested about 500 mg of magnesium daily. Neither received vitamin D supplements. Similarly, the patient reported by Hummel *et al.* (1936, Table 2-6) had high average daily magnesium intakes of 590–615 mg/day during the last two months of pregnancy, the month in which Toverud and Toverud did their metabolic studies (Table 2-5, 2-6), and then

TABLE 2-6. Average Magnesium, Calcium, and Phosphorous Retentions in Pregnancy in a Healthy Quadripara[a]

Month of pregnancy	Magnesium (mg/day)		Calcium[b] (mg/day)		Phosphorus (mg/day)	
	Intake	Retention	Intake	Retention	Intake	Retention
4–5[c]	590	+42	2976	+260	2708	+244
>5–6[c]	590	+104	3022	+238	2600	+356
>6–7[c]	614	+128	3050	+352	2768	+296
>7–8[c]	590	+85	3132	+346	2700	+238
>8–9[d]	615	+104	3191	+401	2633	+201
TOTAL GAIN (final 165 days):	15.5 g		52.9 g		37.1 g	

[a] From data in Hummel *et al.* (1936).
[b] Predominantely from 2 quarts of milk/day and 800 IU vitamin D_3/day (cod liver oil in milk).
[c] Average of 5 metabolic balance periods, averaging 5 days each.
[d] Average of 8 metabolic balance periods, averaging 5 days each.

TABLE 2-7. Average Magnesium, Calcium, and Phosphorus Retentions during the Last 65 Days of Pregnancy in an 18-Year-Old Primipara with a Poor Nutritional History[a]

Days antepartum	Magnesium (mg/day)		Calcium (mg/day)		Phosphorus (mg/day)	
	Intake	Retention	Intake	Retention	Intake	Retention
69–50 (4 metabolic periods)	403	+58	1938	+620	1920	+127
49–25 (5 metabolic periods)	392	+102	1956	+842	1922	+344
24–5 (4 metabolic periods)	375	+25	1950	+648	1965	+283
TOTAL GAIN in 65 days:	4.2g		46.3 g		+ 16.2 g	

[a] From data in Hummel *et al.* (1937).
[b] Predominantly from about 1½ quarts of milk, containing 200 IU vitamin D.

retained an average daily amount of magnesium of 85–104 mg. The poorly nourished primipara whose metabolic balance determinations were performed from 60 to 5 days antepartum (the length of gestation was not specified) exhibited greater daily calcium retention and lesser daily magnesium retentions during most of the metabolic balance periods. Only during two of the periods did she retain more than 100 mg of magnesium daily. Calculations of the retention of the well-nourished quadripara during the 65 days up to 5 days before delivery, to obtain figures comparable to those for the 65-day period during which the young primipara was studied, show that the total gains during the last two months of pregnancy up to five days before birth were:

Element (g)	Primipara	Quadripara
Magnesium	4.2	8.0
Calcium	46.3	25.3
Phosphorus	16.3	12.7

Provocative is the finding that the primipara retained about half as much magnesium and almost twice as much calcium as did the healthy thirty-seven-year-old mother of three healthy children. The greater magnesium retention of the older woman is readily understandable on the basis of her having regularly ingested almost 200 mg more magnesium daily than did the young girl. Her lesser retention of calcium is surprising in view of her having regularly ingested extremely high amounts of calcium (about 3 g daily), in contrast to the acceptable intakes of close to 2 g daily by the young girl.

The magnesium intake of the woman who had had successful pregnancies and healthy offspring (Hummel *et al.*, 1936) is reminiscent of the early metabolic studies by Landsberg (1914). In both, all of the metabolic balance determinations showed retentions of magnesium, as well as of calcium and phosphorus. Since Landsberg's 1914 study in Germany, analysis of self-selected diets of pregnant women have shown that daily intakes of magnesium ranged from 260 mg to below 400 mg in 9 out of the 12 studies evaluated (Coons and Coons, 1935). Two subjects ingested 413–422 mg daily; only one selected a diet that delivered 500 mg/day. The calcium and phosphorus intakes were usually close to the recommended amounts. A recent study of 47 pregnant women residing in Wisconsin (N. Johnson and Phillips, 1976/1980) showed that their daily intake was even less adequate than had been cited in the 1935 study. Their magnesium intakes ranged from 103–333 mg/day, averaging 204 mg± 54 S.D. daily. None ingested the recommended 450 mg/day; 98% ingested less than 70% of the recommended daily allowance; and 79% ingested less than 55%. The lower magnesium intakes were correlated with low birth weights. Ashe *et al.* (1979) have recently shown similarly low intakes in middleclass pregnant women. They had an average daily loss of 40 mg of magnesium.

2.2. Fetal Magnesium Requirements

Coons *et al.* (1935) tabulated the mineral constituents of fetuses by lunar month, obtained from the literature. Table 2-8 provides their magnesium, calcium, and phosphorus data. It should be kept in mind that human fetuses available for such analyses are usually obtained as a result of abnormalities during pregnancy or labor. Thus, their constituents cannot be considered indicative of those of normal fetuses or full-term infants. As an example, among the analyses by Givens and Macy (1933) were twins born after eight lunar months: one died in three hours and had a total magnesium content of 670 mg; the other died after four days and had a total magnesium content of 1443 mg, far more than might be retained in those few days. Magnesium balance data tabulated for newborn infants (Duckworth and Warnock, 1942), suggest total daily retentions of magnesium of 10–18 mg). Thus, the mineral contents of fetuses and neonates have a wide range at any given age, possibly reflecting maternal stores and intake and placental integrity. Widdowson and Spray (1951) analyzed the mineral content of fetuses, tabulating the data by body weight. The data on magnesium, calcium, and phosphorus are given in Table 2-9. The increments of minerals reflect both the growth and changing chemical composition of the fetus as it develops. Widdowson and Dickerson (1962) have illustrated the changes by comparing the composition of a fetus weighing 175 g with its com-

TABLE 2-8. Magnesium, Calcium, and Phosphorus of Fetuses[a]

Age of fetus (lunar month)	Magnesium (mg)			Calcium (mg)			Phosphorus (mg)		
	Number of fetuses	Average fetal content	Daily deposit	Number of fetuses	Average fetal content	Daily deposit	Number of fetuses	Average fetal content	Daily deposit
3	7	15	0.5	10	110	2			
4	3	58	1.5	18	530	15	2	22	0.5
5	10	48	Not done	12	1,970	51	4	680	23
6	8	100	1.8	9	3,510	55	6	1,630	34
7	6	173	2.6	9	7,240	137	6	2,760	40
8	8	306	4.7	7	8,790	55	6	4,400	58
9	7	512	7.4	1	15,140	225	5	5,550	41
10	1	452		11	23,720	306	1	9,420	138
	10	703	9.0				11	14,000	168
MAXIMUM AT TERM:		886			33,370			18,680	

[a] From data in Coons *et al.* (1935).

TABLE 2-9. Magnesium, Calcium, and Phosphorus in Human Fetuses and Full-Term Neonates[a]

Body weight (g)	Magnesium	Calcium	Phosphorus
	(g/kg free body tissue)		
11.1	.08	1.66	1.75
32.5	.12	2.57	2.47
198	0.22	4.57	3.18
225	0.19	4.23	3.12
271	0.15	3.02	2.32
286	0.20	4.72	3.47
314	0.18	4.55	3.22
400	0.15	4.25	3.10
478	0.17	4.38	3.02
673	0.16	5.70	3.55
787	0.21	6.12	3.71
911	0.21	5.68	3.46
1966	0.22	7.90	4.43
2295	0.23	7.75	4.79
2652	0.21	8.08	4.10
3050	0.23	8.75	5.28
3090	0.26	9.70	5.20
3105	0.27	9.35	5.80
3767	0.25	8.80	5.48
3994	0.28	10.30	5.65
4373	0.27	10.30	6.02

[a] From data in Widdowson and Spray (1951) and Widdowson and Dickerson (1962).

TABLE 2-10. Changes in Total Amounts of Magnesium, Calcium, and Phosphorus with Fetal Growth and Maturation[a]

Stage and weight	Magnesium (g)	Calcium (g)	Phosphorous (g)
175-g fetus	.024	0.60	0.42
175-g fetus × 20	.47	12.0	8.4
3.5-kg full-term baby	.76	28.2	16.2
1.5-kg premature baby	.32	10.2	6.5
2.5-kg premature baby	.58	19.0	11.9

[a] Widdowson and Dickerson (1962).

position at 3.5 kg, were its chemical composition to be increased proportionally twentyfold, and the actual composition of a 3.5-kg infant (Table 2-10). Infants born prematurely have considerably less of these minerals than do full-term infants, with relatively lesser amounts of calcium and phosphorus than of magnesium, indicating the lesser bone calcification, most of which occurs in the third trimester. The magnesium content of neonates has been as low as 277 mg and as high as 886 mg; similarly, the calcium content of the newborn has been from 13.08 to 33.27 g, and that of phosphorus, 8.96–18.68 g (Coons *et al.*, 1935).

2.3. Magnesium Serum Levels in Normal and Abnormal Pregnancy

2.3.1. Normal Pregnancy: Magnesium Levels

When the dietary intake of magnesium is not sufficient to meet the demands of gestation, the maternal stores are mobilized and magnesium deficiency can develop. Although under most circumstances the body maintains plasma magnesium levels within very narrow limits, the pregnant woman tends to develop lower than normal magnesium levels, even in the absence of toxemia. Since the homeostasis of calcium and phosphorus is intimately related to that of magnesium, brief note is taken here of the tendency also toward declining calcium levels during pregnancy (Newman, 1957; Hardy, 1956; E. Dawson *et al.*, 1969; Watney *et al.*, 1971). It has been shown that phosphorus levels also fall somewhat during pregnancy, so calcium supplements have often been given in the form of the phosphate, with resultant increase in leg cramps of pregnancy. Hardy (1956) and Kerr (et al. (1962) demonstrated that when the phosphate salt is given, with or without vitamin D_2 (viosterol), the serum total and ionized calcium levels were actually depressed, as compared with the rises seen in pregnant women given calcium carbonate or lactate. Even the serum phosphate levels increased when the nonphosphate calcium salts were given (Kerr *et al.*, 1962). Since high phosphate intake interferes with magnesium, as well as calcium absorption, it is possible that calcium phosphate salts also lowered magnesium levels, and that this might have contributed to the muscle cramps.

The first reports of blood magnesium levels during pregnancy were in 1923. Krebs and Briggs (1923) reported a range of 1.7–2.2 mEq/liter among 17 women in their 8th to 40th weeks of pregnancy. Bogert and Plass (1923) compared the serum

levels of 40 pregnant women at different stages of pregnancy with those of nonpregnant women and found that the average value 2.0 mEq/liter at the outset (which equalled the control average) fell to an average of 1.7 by the end of pregnancy. Watchorn and McCance (1932) found that half of the 12 pregnant women in their series had serum magnesium levels below 1.99 mEq/liter (which was below the values they found in normal nonpregnant subjects), and that the percentage of the total magnesium in the ultrafiltrable fraction was increased. They were dubious that the difference was due to diminished quantities of serum protein, this not being a constant finding, and speculated that an unidentified change in the physicochemical equilibria must have taken place that allowed for more ready passage of magnesium across the placental barrier. Such a change might allow, too, for more ready urinary excretion and might partially explain the need for high magnesium intake during pregnancy to maintain the degree of positive balance necessary for successful gestation without prejudicing the health of the mother. Another group of investigators reported that the blood magnesium of 75 women was higher especially in the sixth month of gestation (range during pregnancy 1.95–2.78 mEq/liter mean = 2.41) than it was four nonpregnant women (2.11 mEq/liter) (Zaharescu-Karaman *et al.*, 1936a). However, they found that the level dropped markedly at the end of labor, to a range of 0.35–2.35 mEq/liter and a mean of 1.5 (Zaharescu-Karaman *et al.*, 1936b). Extremely low serum magnesium levels (1.0–1.1 mEq/liter) were reported in a small series of cases by Wolff and Jorrand Bourquard (1937) in the second month of pregnancy which increased slightly (to 1.25–1.41 mEq/liter) at the end of gestation. Their control (nonpregnant) mean value was 1.7 mEq/liter. Haury and Cantarow (1942) included four normal pregnant women in their tabulation of 108 subjects, and reported a range of 1.4–2.1 mEq/liter; most of their normal controls had serum magnesium levels of 1.8–2.4 mEq/liter. Köberlin and Mischel (1958) also reported lower Mg levels in the first trimester than later in pregnancy. A more extensive report by Newman (1957) has shown the range of serum magnesium levels in 27 normal pregnant women to be very wide in each of the trimesters, at delivery, and at 3–5 days and 6 weeks postpartum (Table 2-11). Newman also

TABLE 2-11. Serum Magnesium, Calcium, and Phosphate Levels During Normal Pregnancy and at Delivery[a]

	Serum magnesium (mEq/liter)	Serum calcium (mEq/liter)	Serum HPO_4^{2+} (mEq/liter)
1st trimester	1.34–2.2 (Av. = 1.57)	4.45–5.55 (Av. = 4.94)	1.45–2.6 (Av. = 1.95)
2nd trimester	1.14–1.8 (Av. = 1.53)	4.1–5.5 (Av. = 4.81)	1.2–2.3 (Av. = 1.78)
3rd trimester	1.03–1.74 (Av. = 1.47)	4.15–5.05 (Av. = 4.69)	1.3–2.6 (Av. = 1.82)
Delivery	0.75–1.73 (Av. = 1.41)	4.3–5.5 (Av. = 4.86)	1.3–2.3 (Av. = 1.93)
Postpartum			
3–5 days	1.04–1.65	4.3–5.95	1.7–3.0
6 weeks	1.2–1.82	4.8–5.3	1.75–2.6

[a] Twenty-seven women; data from Newman (1957).

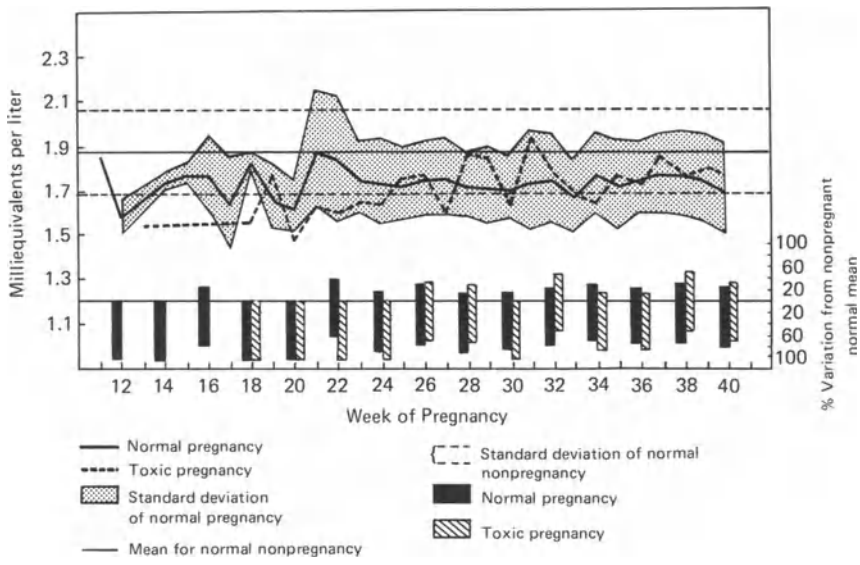

FIGURE 2.2. Comparison of serum magnesium values in toxic and nontoxic pregnant women. (From DG Hall: *Obstet Gynec* 9:158–162, 1957.)

reported an unusually wide normal range of serum magnesium (1.34–2.4) in nonpregnant women. The calcium and phosphorus levels also dropped slightly.

Hall (1957) graphed values, obtained from 30 pregnant patients who were followed from 11 weeks to term and at six weeks postpartum (Fig. 2-2), as well as values from 294 normal and toxemic (11.9%) women. Their work illustrates that the normal pregnant woman tends to have serum magnesium levels that remained at the low limit for the nonpregnant range (1.69–2.0 mEq/liter) with the broadest range (about 1.6–2.1) in the second trimester. The lowest values that were recorded in this study, which started in the 11th week, were in the 12th–18th week of pregnancy (1.45–1.8 mEq/liter. Achari *et al.* (1961) found no difference in serum magnesium levels of normal pregnant and nonpregnant women; both groups had a range of 1.5–1.9 mEq/liter. DeJorge (1965a,b) found that serum magnesium levels fell continuously in 99 pregnant women from about 1.6 mEq/liter in the second month to about 1.2 mEq/liter in the eighth month, as compared to their nonpregnant range of 1.70–2.25 mEq/liter. Correcting for the dilution of plasma that occurs during pregnancy, in a study of 139 pregnant women (Table 2-12), they concluded that the hypomagnesemia is real only during the first half of pregnancy and during the last month (DeJorge, 1965b). Comparable conclusions were reached by Dawson *et al.* (1969) in their study of 244 adolescent (ages 13–19) pregnant women. The mean plasma magnesium levels declined slightly from 2.6–2.2 mEq/liter as pregnancy progressed, but showed no change when expressed as a ratio to hematocrit values.

Celli Arcella (1965) reported lower serum magnesium levels (1.9 mEq/liter) during the third trimester than in normal nonpregnant women (2.2 mEq/liter). Lim *et*

al. (1969b) similarly reported significantly lower serum (and erythrocyte) levels in normal pregnant women in the third trimester than in normal nonpregnant women. In the latter study, the average of 105 serum samples from normal pregnant women was 1.43 ± 0.05 mEq/liter, with a range of 1.28–1.73, as compared to the normal nonpregnant value of 1.60 ± 0.17. The average value for erythrocyte Mg was also lower than for nonpregnant women. The authors suggest that these differences, taking into account the increasing demands of the rapidly growing fetus, may indicate an occult magnesium deficiency. In contrast, Mahran and Hanna (1968) reported a higher mean (1.83 ± S.D = 0.28) among normal pregnant women in the third trimester, as compared with their control mean magnesium value of 1.66 mEq/liter ± S.D = 0.01. They expressed concern about the magnesium deficiency early in pregnancy, at a time when hyperemesis gravidarum can lead to loss of minerals, including magnesium. They stressed the importance of repairing the magnesium deficit, as well as that of the fluids and more commonly considered electrolytes. This observation recalls the work of Hall (1957), who showed the lowest serum magnesium levels in the early weeks of his study, and that of DeJorge (1965b), who considered the magnesium deficit real only in the first half of pregnancy and the final month.

The change in serum magnesium that takes place during labor and in the parturient period are not clear. Wallach *et al.* (1962) found the concentrations of plasma Mg to be below normal in three normal parturient women (1.57–1.70 mEq/liter), as compared with the normal value of 2.0 ± 0.15, obtained from 75 men and women 19–68 years of age. Celli Arcella (1965) reported that serum magnesium levels rose to normal levels during labor, after the low values they had noted during the third trimester. Lupi *et al.* (1967) noted low serum magnesium levels (1.4 mEq/liter) at the beginning of labor, but observed a further decline during the final stage of labor (1.1 mEq/liter). Manta *et al.* (1967) also found serum magnesium levels to decrease during labor, reaching the lowest point at the stage of expulsion and then rising. These findings confirm the early report that the mean serum magnesium

TABLE 2-12. Magnesium Serum Levels in Pregnant Women, as Measured and Corrected for Hemodilution[a]

Gestation (days)	Magnesium levels in serum laboratory report (mEq/liter ± S.D.)	Corrected for hemodilution (mEq/liter ± S.D.)
0–30	1.87 ± 0.10	1.83
31–60	1.83 ± 0.10	1.79
61–90	1.73 ± 0.09	1.77
91–120	1.69 ± 0.14	1.91
121–150	1.60 ± 0.18	1.96
151–180	1.56 ± 0.10	2.05
181–210	1.49 ± 0.10	2.08
211–240	1.53 ± 0.12	2.16
240–270	1.39 ± 0.17	1.88
Nonpregnant	2.09 ± 0.07	

[a] From DeJorge *et al.* (1965).

levels drop at the end of labor to 1.5 [range = 0.35–2.35 mEq/liter (Zaharescu-Karaman, 1936b)], and those of Rusu *et al.* (1971/1973), who found that the mean serum magnesium levels dropped slightly at the outset of labor in 38 women to 2.0 mEq/liter from 2.3 just before labor began. During active labor there was a further drop (in 88 women) to 1.5 ± 0.3 mEq/liter. Ten women with imminent premature labor had a mean serum level of 1.4 ± 0.3 mEq/liter. The values depicted in Table 2-13 indicate that most investigators have found low maternal serum levels at delivery, cord blood values being significantly higher.

TABLE 2-13. Serum Magnesium Levels in Maternal and Cord Blood[a]

Investigator(s)	Method	Maternal (at delivery)	Cord blood
Bogert and Plass (1932)	Phosphate precipitate	1.7 (1.2–2.6)	1.8 (1.2–2–8)
DeToni (1932)	" "		2.9
Zaharesco-Karaman *et al.* (1936b)	" "	1.5 (0.4–2.8)	2.0
Marioni *et al.* (1951)	" "	1.5 (1.0–1.8)	1.5 1.0–1.9)
Salmi (1954–1955)	" "	2.2 (1.4–2.9)	2.3 (1.2–3.3)
Carletti and Rosti (1963)			1.0–2.5
Brunelli *et al.* (1966)	" "	Toxemic 1.4 ± 0.46 Normal 1.5 ± 0.32	1.4 ± 0.46 1.5 ± 0.34
Newman (1957)	" "	1.4 (0.8–1.7)	1.6 (1.3–1.7)
Zytkewicz *et al.* (1965)	" "	1.7 ± 0.20	No data
Acharya and Payne (1965)		No data	(1.1–1.5)
Ferlazzo *et al.* (1965)		" "	1.7 (1.3–2.1)
Bajpai *et al.* (1966)	Xylidyl blue	" "	1.6 (1.5–1.8)
Takashi *et al.*, (1967)		1.5	1.6
Avezzu *et al.* (1969)		1.6	1.5
Engel and Elin (1970)	Atomic absorption	No data	Normal 1.59–0.28 Low Apgar 1.95 ± 0.4
Watney*et al.* (1973)	" "		1.7
Tsang *et al.* (1973)	" "	1.4–1.5	1.6–2.0
Snodgrass *et al.* (1973)			
Jukarainen (1974)	" "		(Venous) 1.61

[a] Mean or average and range: mEq/liter.

Caddell *et al.* (1973a) have evaluated the magnesium status of postpartum, well-fed women in Thailand (where the magnesium intake is greater than it is in the United States), and found that the postpartum plasma magnesium levels were significantly lower than they were in young nulliparous women. When they were tested by a parenteral magnesium load, the postpartum women retained a mean of 15% more magnesium than did the nulliparous women (borderline significance). Some apparently normal, asymptomatic postpartum patients had moderately high magnesium retention, but 37% retained only 0–25%. In a study of 198 moderate-income American mothers assessed by an intravenous magnesium load test, the mean postpartum magnesium retention was 51% (Caddell *et al.* 1975). Over 90% of the magnesium load was retained by biologically immature (under 17 years of age) multiparas and in young mothers of twins. Most primiparous mothers showed little retention of the load, but 6 who had had prolonged labors retained 78% of the load. Multiparous mothers with a long interval since the previous pregnancy had the lowest magnesium retention. However, among the 46 patients who retained less than 40% of the load, the mean plasma magnesium was 1.58, and among the 81 who retained more than 40%, the plasma magnesium was 1.45 mEq/liter. Only plasma levels below 1.2 mEq/liter could be matched with high retention of magnesium.

2.3.2. Preeclampsia and Eclampsia: Magnesium Levels and Treatment

The use of magnesium salts parenterally for control of manifestations of acute eclampsia long antedated the demonstration that serum levels of magnesium tend to be lower in women with toxemic pregnancies (especially early in the course of pregnancy) than they are during normal pregnancies. Less reliable as an index of magnesium deficiency of toxemic pregnancy is the serum level toward the end of gestation, when renal damage can interfere with magnesium excretion, as it does in patients with nephritis. The first published reports of the anticonvulsant properties of magnesium sulfate in eclampsia appeared in Europe (Einar, 1907; Kaas, 1917). It became a favored treatment of convulsions of pregnancy in the United States from the time Lazard (1925) and McNeile and Vruwink (1926) recommended its use intravenously, Dorsett (1926) described its use intramuscularly, and Alton and Lincoln (1925) reported its use intrathecally. Hirschfelder (1934) first reported a markedly low serum magnesium level (0.8 mEq/liter) in a 47-year-old patient with eclampsia, who then responded favorably to high dosage oral magnesium sulfate therapy. Among eight eclamptic women, Haury and Cantarow (1942) reported three with serum magnesium levels of 0.8–1.0 mEq/liter and three with levels of 2.7–3.2 mEq/liter. Their stages of pregnancy were not given. Achari *et al.* (1961) reported that 21 eclamptic women had a mean serum magnesium level of 0.83 mEq/liter (range = 0.25–1.84). Eclamptic women frequently have higher plasma or serum magnesium levels toward the end of pregnancy than do normal pregnant women at term

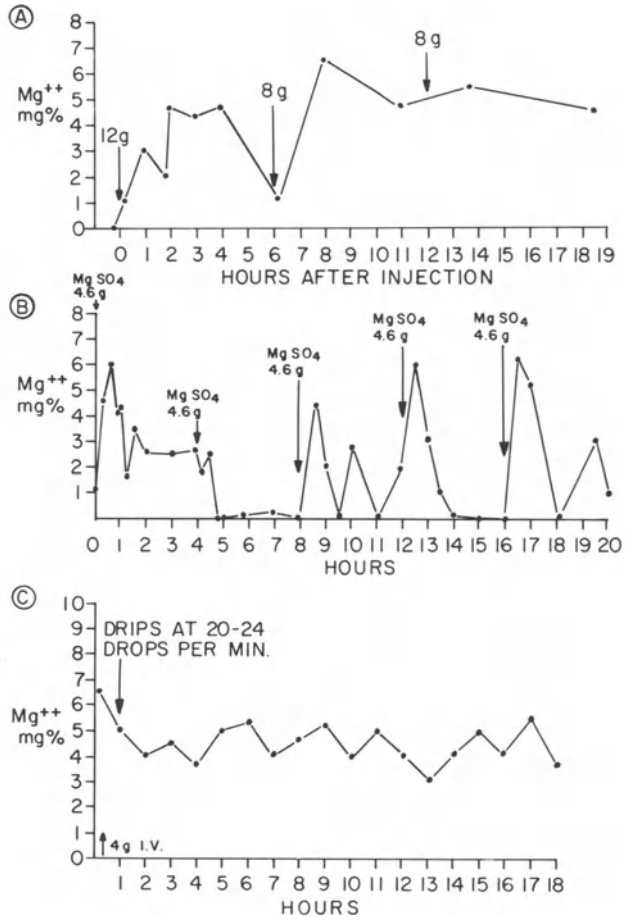

FIGURE 2-3. Plasma magnesium levels following magnesium therapy for eclampsia. A: Following intermittent I.M. $MgSO_4$. B: During intermittent I.V. $MgSO_4$. C: During continuous I.V. 1.5% $MgSO_4$ I.V. (From CE Flowers Jr *et al.*: *Obstet Gynec* 19:315–327, 1962.)

(Pritchard, 1955; Hall, 1957; Kontopoulos *et al.* 1976/1979), but such normal or even elevated levels are not considered a contraindication to the use of large doses of magnesium salts, which are administered parenterally for their pharmacodynamic neurosedative, antihypertensive effects and not to correct a deficiency. As much as 200 mg of magnesium an hour, given intravenously as the sulfate, was recommended in the early studies (Lazard, 1925, 1933; McNeile, 1934; Winkler *et al.*, 1942). This route is recommended by many either as the sole approach (Zuspan and Ward, 1964, 1965; Zuspan, 1966, 1969; Harbert *et al.*, 1968; Hutchinson *et al.*, 1963), or in combination with intramuscular injections (Pritchard, 1955; Flowers *et al.* 1962; Flowers, 1965, 1975; Kontopoulos *et al.*, 1976/1980, Weaver, 1976/1980; Flowers *et al.*, 1962, Fig. 2-3). Pritchard (1955) observed that administration of

large doses of epsom salts orally exerted no effect on the plasma magnesium levels. Since only 5% of the administered dose appeared in the urine, the possibility that only a small percentage of the administered dose was absorbed was considered. However, even after administration of 150 g of magnesium sulfate intramuscularly over a five-day period, he found that the plasma levels were maintained between 3.5 and 7 mEq/liter. When treatment was initiated with 4 g of $MgSO_4$ intravenously, there was an initial peak, followed by a prompt rapid fall and then a gradual decline. He found that the cerebrospinal fluid magnesium levels did not reflect the high plasma levels induced by therapy. Flowers (1965) found it necessary to use a mean of 70 g of magnesium sulfate over a three-day period to control eclampsia. Similarly, Harbert *et al.* (1968) found it necessary to use 40–60 g of magnesium sulfate per 24 hours to maintain neurosedative serum levels of magnesium of 6–8 mEq/liter. Perhaps the failure to develop hypermagnesemia more frequently toward the end of an eclamptic pregnancy and the difficulty in maintaining pharmacologic blood levels may reflect not only repletion of maternal stores but high fetal requirements, which might not have been supplied during the abnormal pregnancy.

2.3.2.1. Possible Contribution of Magnesium Deficiency to Eclamptic Pregnancy

Hall (1957), because of the experimental and clinical evidence that magnesium deficiency is associated with neuromuscular irritability and convulsions, and because of the long-recognized efficacy of magnesium in the management of preeclampsia and eclampsia, considered the possibility that magnesium deficiency might contribute to toxemia of pregnancy. He found that the mean of plasma mangesium levels had been somewhat lower among toxemic than among normal pregnant women from the 12th through the 25th week. He charted a tendency of the magnesium levels to rise slightly toward the end of pregnancy in toxemic women (Fig. 2-2, Hall, 1957), a finding that might be related to increasing renal damage in that group. The percentage variations from the normal nonpregnant levels were as great as 50%–90% below the mean at different times during pregnancy. However, since the differences between the levels in the normal and toxemic pregnant women were not statistically significant, Hall questioned whether the low magnesium levels contributed to the symptoms of toxemia. Two years earlier a preeclamptc woman with pseudohypoparathyroidism (serum calcium of 4–6 mg percent and lack of response to PTH), and hypomagnesemia (1.1 mEq/liter) associated with mental aberrations, had been reported from the same medical center (Suter and Klingman, 1955). The possibility was considered that lowered serum magnesium levels during pregnancy might predispose to seizures during pregnancy in susceptible women, such as those with a tendency toward epilepsy (Suter and Klingman, 1957). Flowers *et al.* (1965) suggested that depletion of tissue stores of magnesium might explain eclamptic patients' tolerance and requirement for such large doses of magnesium. McGanity (1965) proposed that dietary magnesium deficiency might be etiologic in preeclampsia.

In France, where latent tetany had long been recognized as a manifestation of

subacute magnesium deficiency (Durlach and LeBrun, 1959; 1960; Durlach, 1969a), uterine cramps and abnormal contractility during pregnancy have been shown to be responsive to treatment with magnesium, and have been proposed as a manifestation of its deficiency (Dumont, 1965; Muller, 1968; Muller *et al.*, 1971/1973).It was observed that patients with this complaint frequently also exhibited latent tetany and often had marginal hypomagnesemia (1.5 mEq/liter or lower levels), with and without hypocalcemia (Dumont, 1965). Uterine hypercontractility has been added to the signs of toxemia of pregnancy and has also responded to intravenous magnesium therapy (Hutchinson *et al.*, 1963; Cobo, 1964).

The efficacy of pharmacologic doses of magnesium in the treatment of manifestations of toxemias of pregnancy has led to consideration of magnesium as a drug, in that condition, far more commonly than consideration of the fact that it is a nutrient, the supply of which must be increased substantially during gestation. Two years before hypomagnesemia was first reported in an eclamptic woman (Hirschfelder, 1934), magnesium deficiency was associated with abnormalities of pregnancy and during early lactation in cows (Sjollema, 1932). Neuromuscular manifestations in pregnant and lactating herbivores included tetany and convulsions; cardiovascular lesions were found at autopsy (Sjollema, 1932; Rook and Storry, 1962; Storry and Rook, 1962; Rook, 1963; Herd, 1966a,b; Hjerpe, 1971). Magnesium deficiency has been accepted as contributory to toxemia of pregnancy in grazing animals, and magnesium recognized as protective.

The possibility is increasingly being considered that magnesium deficiency can also contribute to major and lesser manifestations of toxemias of pregnancy (Dumont, 1965; McGanity, 1965; Lim *et al.*, 1969b; Muller, 1968; Muller *et al.*, 1971/1973; Hurley, 1971; Seelig, 1971; Seelig and Bunce, 1972; Kontopoulos *et al.*, 1976/1980; Weaver, 1976/1980). There is evidence that the magnesium intake during pregnancy is likely to be suboptimal (Review: Seelig, 1971). That it might be sufficiently low to contribute to early and late abnormalities of pregnancy is suggested by the survey that showed magnesium intakes during pregnancy that are low (N. Johnson and Philipps, 1976/1980), even by standards for nonpregnant women (Seelig, 1964). The women with the lowest magnesium intakes gave birth to low-birthweight infants, a finding that suggests intrauterine growth retardation. Mahran and Hanna (1968) expressed concern about the magnesium deficit, early in gestation, that might be caused by hyperemesis gravidarum. When one considers how frequently lesser degrees of nausea and vomiting (i.e., "morning sickness") interfere with proper nutrition in the first trimester, and one recalls the evidence that hypomagnesemia is encountered at that time (de Jorge *et al.*, 1965a,b) and shortly thereafter (Hall, 1957), the possibility of early magnesium deficiency being etiologic in abnormalities of pregnancy, placental abnormalities, intrauterine malnutrition, and fetal abnormalities should be seriously entertained. That hyperemesis can precipitate acute hypomagnesemia later in pregnancy was demonstrated in a report by R. Fraser and Flink (1951) of a 33-year-old woman who developed hypochloremic, hypokalemic alkalosis in association with hypomagnesemia a few days before delivery of her eighth child. It should be noted that so young a woman, completing her eighth pregnancy, would be expected to be magnesium depleted.

2.3.2.2. Possible Contribution of Magnesium Deficiency to Placental and Coagulation Abnormalities

The abnormalities of placentas of eclamptic women which range from functional insufficiency (secondary to arteriolar spasm) to small size, scarring, and infarction (Warkany *et al.*, 1961: Holman and Lipsitz, 1966; Wigglesworth, 1966) are associated with intrauterine growth retardation (IUGR) and hypoxia. There is insufficient evidence to implicate magnesium deficiency in eclamptic pregnancy as a direct contributory factor in placental abnormalities, but there are some findings that suggest the need for further study of this question. Charbon and Hoekstra (1962) tabulated the magnesium and calcium contents of placentas from women with normal single and twin pregnancies and with preeclampsia or eclampsia. The decreased magnesium and increased calcium levels of the placentas from eclamptic women are especially striking (Table 2-14). Magnesium-deficient pregnant rats had placental calcification and bore low-weight young (Cohlan *et al.*, 1970; Dancis *et al.*, 1971). An excess of vitamin D, which is known to cause net loss of magnesium (to be discussed later in this volume) has caused reduction in placental size in rats, placental damage, and birth of small for gestational-age young (Potvliege, 1962; Ornoy *et al.*, 1968). Whether the peroxidized cod liver oil, or its fractions, that were used to produce experimental eclampsia in rats, with intravascular coagulation and damaged placental trophoblast (McKay *et al.*, 1967) also cause magnesium loss has yet to be investigated. Changes similar to those caused by an excess of vitamin D or peroxidized vitamin D have been reported in placentas of women with eclampsia, and thrombocytopenia that reflects intravascular platelet aggregation of eclampsia has long been recognized (Review: McKay *et al.*, 1967).

The initiating factor that damages the syncytial trophoblast in human preeclampsia is not known. Hyperreactivity to vitamin D, possible formation of toxic derivatives of that sterol (Seelig and Mazlen, 1977), and the evidence that high Ca/Mg and Na/K ratios increase arterial resistance (Haddy and Seelig 1976/1980) are factors that should be considered. It remains to be resolved whether the observation that magnesium administration to preeclamptic women produced highly significant increased coagulation time and decreased platelet adhesiveness (Weaver, 1976/1980) indicates only a direct effect of magnesium on coagulopathy, or whether it plays a role in correcting a deficit that intensifies placental damage.

The coagulation abnormalities of eclampsia (McKay *et al.*, 1967; Howie *et al.*, 1976), the significant risk of antenatal thromboembolism (Editorial, *Brit. Med.*, 1:249–250, 1970), and the hypercoagulability of the blood of eclamptic patients who

TABLE 2-14. Calcium and Magnesium Content of Placentas[a]

	Normal	Twins	Preeclampsia	Eclampsia
Magnesium (mg/100 ml)	8.87	6.94	6.49	4.30
Calcium (mg/100 ml)	86.4	124.6	94.2	134.6

[a] Tabulated by Charbon and Hoekstra (1962) from Mischel (1957).

have responded to magnesium therapy (Weaver, 1980) are provocative observations pointing toward a possible etiologic role of early magnesium deficiency. Perhaps the clinician is in error when he assumes that the hypomagnesemia seen during normal pregnancy is necessarily normal. It would have been useful had serum magnesium levels been obtained from the thriving mother whose sustained positive magnesium balance throughout pregnancy has been described by Hummel *et al.* (1936). Her daily intake of magnesium had exceeded the generally recommended 400 mg/day by 200 mg daily; she had retained 15½ g of magnesium during the last half of her pregnancy. If the magnesium requirements during pregnancy are as great as those suggested by the early Landsberg (1914) study and those of Hummel *et al.* (1936, 1937), and if magnesium deficiency contributes to toxemia, why is toxemia not more common? The answer may lie in the possibility that unlike the magnesium-deficient pregnant rats that sustain their own magnesium levels, with fetal loss, the normal less depleted woman draws more on her own reserves of magnesium to meet fetal demands. Her declining blood levels may reflect the drain, but need not be associated with maternal pathologic changes unless concomitant abnormalities are present. If the rat studies are relevant to pregnant women, it may be that in some women with insufficient magnesium deficiency to cause overt maternal changes, there can be fetal damage, in view of high fetal cellular demands for magnesium (McCance and Widdowson, 1961).

Already mentioned is the possibility that agents (such as vitamin D or derivatives) that affect magnesium requirements, as well as presenting other toxic potential (Seelig and Mazlen, 1977), can participate. Additionally, in a study of the effect of vitamin D_2, with and without calcium and phosphorus supplements on success of gestation in rats, Nicholas and Kuhn (1932) found that unlike the test rats the control rats were given fresh green vegetables, yeast, fruits, butter, and cod liver oil and had the best gestations. Thus, the controls received a balanced diet containing magnesium, trace elements, the B vitamins, and vitamin A, which were absent in the experimental groups that had significantly less successful gestations. This study calls to mind the studies implicating pyridoxine deficiency in the "morning sickness" syndrome and in later manifestations of toxemia (Sprince *et al.*, 1951; Klieger *et al.*, 1966). The extent to which magnesium and pyridoxine deficiencies might interrelate in pregnancy—both nutrients are involved in phosphorylation reactions and protein synthesis (Review: Durlach, 1969b)—remains to be determined.

Even such a seemingly minor abnormality as a smaller than normal placenta has been associated with a disproportionate reduction in birth weight (Wigglesworth, 1966). Placental infarction, such as occurs in toxemic pregnancy, interferes with placental transfer of nutrients and affects gaseous diffusion, leading to lowered oxygen levels in the fetus. Scarred placentas have impaired blood flow, with resultant retardation of intrauterine growth and oxygenation (Walker and Turnbull, 1953; Warkany *et al.*, 1961; Gruenwald, 1961, 1963, 1964; Scott and Usher, 1964; Holman and Lipsitz, 1966; Wigglesworth, 1966). Even moderate maternal malnutrition has been shown to be associated with significantly smaller than normal placentas and a high prevalence of low-birth-weight infants (Lechtig *et al.*, 1975). Scott and Usher (1966) analyzed the factors associated with fetal malnutrition and found that it

occurred in 13.5% of the primipara (usually young), and in only 8.4% of multiparous births, but that the incidence rose with each successive pregnancy after the sixth pregnancy. There was also a higher incidence of fetal malnutrition when previous pregnancies had produced low-birth-weight infants, to as high as a ninefold increased incidence when there had been four or more low-birth-weight infants. Infants with IUGR had a higher incidence of fetal distress, asphyxia neonatorum, and congenital abnormalities than did normal-weight infants. Congenital anomalies were diagnosed in 17% of the 60 markedly underweight infants and in 31% of 35 who were markedly wasted. The incidence represents a 30-fold increase in major anomalies and a 16-fold increase in congenital heart disease in infants with marked fetal malnutrition.

Placental insufficiency, found not only in eclampsia and frequent pregnancies but in prolonged gestation, placenta praevia, and pregnancy in the elderly primigravida patient, is associated with fetal malnutrition and low calcium and glucose levels in the infant (Khattab and Forfar, 1971). There should be routine determinations of magnesium levels and retention during and after pregnancy in women at risk of placental pathology, and of their infants.

2.4. *Magnesium Levels in Women with Recurrent or Imminent Abortion*

Women who have experienced one spontaneous abortion not infrequently experience repeated abortions. Zigliara *et al.* (1971/1973) studied the magnesium levels of 294 women with imminent abortions and found that 50% had significantly lower than normal erythrocyte magnesium levels; 25% had hypomagnesemia as measured by serum determinations. The serum levels showed the existence of severe chronic magnesium deficiency in only 11% whereas low erythrocyte magnesium levels were seen in 40.8% of those with repeated abortions. The greater the number of abortions, the greater the degree of magnesium deficiency detected. Normal levels were reached three days after the abortion. Rusu *et al.* (1971/1973) also reported lower (than in normal pregnancy) magnesium levels among women with imminent abortions (1.4 ± 0.3 mEq/liter versus 2.0 mEq/liter). Treatment with magnesium doubled the serum levels and permitted some of the women to continue to term.

Whether the uterine hypercontractility, considered part of the preeclamptic syndrome (Hutchinson *et al.*, 1963; Cobo, 1964) and found as a complication of pregnancy among women with latent tetany of marginal hypomagnesemia (*supra vide*), is related to the hypomagnesemia of recurrent aborters remains to be proved. Rusu *et al.* (1971–1973) found that as the serum magnesium level fell the uterine reactivity to oxytocin increased.

It may be relevant that magnesium-deficient animals have poor gestational success, with evidence of resorption at implantation sites in severely deficient animals, and smaller-than-control size of litters in less deficient animals.

The severity of postpartum uterine cramps has also been related to the drop in serum magnesium after delivery. Nicolas (1971/1973) reported that there was a

slight decrease of magnesium levels during labor [1.74 (1.4–2.2 mEq/liter)] and 24 hours later [1.64 (1.4–2.2)]. A double-blind study in which one group was given magnesium therapy after delivery (500 mg magnesium lactate four times a day) or placebo resulted in a significant ($p < 0.001$) increase of magnesemia (from 1.6 to 1.9) in the magnesium-treated group, a change that was associated with improvement in uterine discomfort; there was no change in uterine cramps in the placebo-treated group.

3
Consideration of Magnesium Deficiency in Perinatal Hormonal and Mineral Imbalances

In view of the evidence that inadequate magnesium intake is common during pregnancy and that the plasma levels of magnesium tend to fall, especially during the first and third trimesters of pregnancy even when corrected for hemodilution, it is not surprising that neonatal magnesium deficiency can create problems. Until relatively recent years, however, measurement of magnesium levels in infants was rare. Cord blood analyses, done at intervals since 1923 (Table 3-1) showed wide ranges reported in individual studies, even when the quite reliable old precipitation methods or the more reliable modern procedures were employed. Since individual maternal status and infant status were not designated in most instances, these wide ranges are difficult to interpret. Low levels may have reflected maternal and fetal insufficiency; high levels may have reflected magnesium therapy for preeclampsia. Mean values are even more difficult to evaluate. Determination of serum or plasma magnesium levels of the infant at birth or within hours thereafter presents more problems. Intrauterine asphyxia, difficulties in delivery, or other causes of birth hypoxia or acidosis, and hyperosmolality can all contribute to elevations of serum magnesium levels as the cellular magnesium is released to the extracellular fluid, changes similar to those seen with surgical and other traumatic shock and hypoxic conditions. Such infants have been found to have a negative correlation between their serum magnesium levels and their Apgar scores (Engel and Elin, 1970; Jukarainen, 1974). Infants who are hypermagnesemic when born shortly after their eclamptic mothers had received pharmacologic parenteral doses of magnesium also are likely to be depressed and have low Apgar scores. The first group of infants is likely to be cellularly depleted of magnesium, which becomes manifest as hypomagnesemia, usually by the fifth day of life. Those with hypermagnesemia following maternal magnesium therapy usually take longer for their serum levels to drop to normal limits. If the infant survives the respiratory depression of pharmacologic

TABLE 3-1. Serum Magnesium in Infancy (Including Cord Blood When Compared with Infant Blood)[a]

Investigator(s)	Method	Cord blood	Infant blood at birth	Serum levels		
				First week	1 mo to 1–2 yr	
Salmi (1954–1955)	PO_4 precip.	2.3 (1.2–1.3)	No data	2.5 (1.9–3.3)	1.6 (1.1–1.9)	at 1–2 mo
Orange and Rhein (1951)	Titan yellow	No data	No data	1.6 (1.3–1.9)		No data
Breton *et al.* (1960)	"	Low birth weight 2.2 (1.8–2.7) Normal 2.7 (1.8–3.3)	"	No data	2.0 (1.5–2.6)	at 1–24 mo
Anast (1964)	"	1.6 (1.1–2.0)	"	1.6 (1.1–2.4)	1.7 (1.5–2.0)	at 1–12 mo
Gittleman *et al.* (1964)	"	No data	"	Day 1: 1.6 ± 0.16		
Ferlazzo *et al.* (1965)		1.7 (1.3–2.4)			1.5–1.7	at 10–30 days
Zytkiewicz *et al.* (1965)	"	"	"	Day 2: low birth weight 1.3 (0.8–1.7) Normal 1.32 ± 0.20		
Siegel and Langley (1964)	EDTA			1.32 ± 0.20		
Mays and Keele (1961)	"	1.14 ± 0.18		No data	1.3 ± 0.13 1.4 ± 0.15	at 1–12 mo at 12–36 mo
Acharya and Payne (1965)	"	1.3–1.8	1.5–2.0	No data	No data	
Bajpai *et al.* (1966)	Xylidyl blue	1.6 (1.5–1.8)	No data	1.5 (1.2–1.8)	No data	
Kobayashi	Fluorometry	No data		0–5 days: 1.6 ± 0.19 6–10 days: 1.5 ± 0.15	1.7 ± 0.17 2–11 ± 0.17	at 11–60 days

Teh (1968)	"	"	1.5 (.05.S.E.)	1.4	2.3 ± 0.15	at 2–11 mo
					1.5 (1 S.E.)	at 2–4 wk
					1.6 (.07 S.E.)	at 2–24 mo
					1.9 (± 0.06)	at 1–10 yr
Harrison (1968)	Atomic absorption and fluorometry	Low birth weight: 1.4 ± 0.08 Normal: 1.5 ± 0.05				
Fomon *et al.* (1969)	"	No data		No data	1.7 ± 0.3	at 28 days
					1.7 ± 0.2	at 56 days
					1.7 ± 0.2	at 84 days
					1.8 ± 0.2	at 112 days
Harvey *et al.* (1970)	"	(0.7–1.3)		Breast-fed: 1.07 (0.76–1.41) Bottle-fed: 0.97 (0.76–1.23)		
Tsang and Oh (1970b)	"	No data		Low birth weight	1.86 ± 0.28	
Paupe (1971)	Bauhon method				1.8 ± 0.15	at 6 mo
Carrero (1971)	No data		1.6 (1.2–3.0)	Days 1–16: 2.5 (1.4–3.0)	2.0	at 1–24 mo
Jukarainen (1974)	Atomic absorption	1.61 ± 0.29 1.83 ± 0.27		Low birth weight: 24–32 hr 1.70 ± 0.27 32–40 hr, 1.83 ± 0.29 16–24 hr, 1.81 ± 0.31 32–48 hr, 1.70 ± 0.26		

[a] Mean or average and range: mEq/liter.

hypermagnesemia, it is moot whether the presumed antenatal magnesium deficiency might have been corrected.

Magnesium determinations during infancy have not been frequently reported; when reported, they have rarely included data on the maternal or infant status (Table 3-1). The first report found was one in which 24 magnesium levels were included in a table of 116 infants and children with a variety of abnormalities whose calcium levels had been analyzed (Denis and Talbot, 1921; Table 3-2). When the syndrome of magnesium malabsorption was recognized and infantile hypocalcemia was found often to be unresponsive to calcium or calcemic agents but to respond to magnesium repletion, magnesium determinations were done more commonly. The change in infant feeding patterns from breast-feeding to use of a variety of formulas has led to increased mineral retentions that are not paralleled by calcium and magnesium plasma levels, which are lower in infants fed cows' milk than in normal infants who are breast-fed.

TABLE 3-2. Hypomagnesemia in Sick Infants and Children[a,b,c]

Sex	Age	Plasma magnesium (mEq/liter)	Plasma calcium (mg/100 ml)	Diagnosis
F	1½ mo	0.65	6.9	Convulsions; mental retardation
M	4 mo	0.83	12.9	[d]
F	4 mo	1.00	9.8	Nephritis[d]
M	4 mo	1.30	8.1	[d]
M	4 mo	1.08	5.6	[d]
M	4 mo	0.83	3.1	[d]
M	4 mo	1.23	1.0	[d]
M	5 mo	0.83	2.5	Convulsions[d]
M	5 mo	0.83	2.0	Convulsions[d]
M	5 mo	0.40	2.9	Tetany[d]
M	7 mo	1.23	2.5	Tetany, rickets, laryngospasm, death
F	7 mo	1.30	6.1	Bronchopneumonia
F	8 mo	0.65	5.3	Convulsions, pneumonia, rickets, anemia
F	10 mo	1.30	8.0	Pneumonia, rickets, thymic enlargement, clubbed fingers
M	10 mo	1.23	1.0	Tetany, microcephalus, rickets[d]
M	11 mo	1.00	10.6	Pneumonia, colitis
M	12 mo	1.06	7.2	Rickets[d]
F	17 mo	1.29	5.0	Pneumonia, empyema, pyelitis
M	3½ yr	1.30	6.3	Encephalitis
F	4 yr	0.80	6.5	Purpura
F	4 yr	0.83	5.0	Epilepsy
M	5 yr	1.33	2.9	Petit mal
F	7 yr	1.00	5.3	Purpura, furunculosis
M	7 yr	1.09	4.8	Chorea

[a] From data in Denis and Talbot (1921).
[b] Hypomagnesemia in 24 of 38 with Mg determinations; 13 had values between 1.67 and 2.67 mEq/liter; one had hypermagnesemia (4.17). (Data abstracted from a table of a series of 116 with Ca analyses).
[c] 1 of 3 infants with hypercalcemia (> 12 mg/100ml) had microcephalus and mental retardation.
[d] Feeding problems listed.

Infants at greatest risk of neonatal hypomagnesemia are low-birth-weight infants, including those suffering from intrauterine growth retardation (IUGR) or premature infants recovering from birth hypoxia or later respiratory distress, and infants born to very young primiparous women or to young mothers who have had frequent pregnancies or multiple births, to preeclamptic mothers, and to diabetic mothers. Plasma magnesium levels are a less reliable index of magnesium deficiency than is the parenteral load test, and magnesium deficiency, so demonstrated, has been found to be more common in newly born premature than in full-term infants, even when not indicated by notable hypomagnesemia (Caddell, 1975). The incidence of neonatal magnesium insufficiency may be greater than suspected. The tendency of women with preeclampsia or eclampsia to develop rising plasma magnesium levels during the last month of pregnancy, even without magnesium therapy, despite which they retain high percentages of parenterally administered pharmacologic doses of magnesium, suggests that magnesium deficiency might be far more common during pregnancy than is indicated by the incidence of hypomagnesemia.

3.1. Magnesium Deficiency during Gestation

3.1.1. Effects of Experimental Maternal Magnesium Deficiency on the Fetus

To attribute the high incidences of placental and fetal abnormalities, stillbirths, and neonatal deaths (found among infants born to eclamptic women) to magnesium deficiency during gestation would be highly speculative at this stage of our knowledge. However, there are provocative findings that point to the possibility that it is likely to be contributory, not only to complications of pregnancy, but to damage to the products of conception. Interrelationships with other factors must be considered.

Rats kept severely magnesium depleted (receiving $^1/_{200}$ the control magnesium intake) for the entire 21-day period of gestation had no living fetuses at term (Hurley and Cosens, 1970, 1971; Hurley, 1971; Hurley *et al.*, 1976). The shorter the duration of the magnesium deficiency, the fewer implantation sites were affected. When the deficiency was maintained from day 6–12, about 30% of the implantation sites were involved and 14% of the full-term fetuses had gross congenital abnormalities (cleft lip, hydrocephalus, micrognathia or agnathia, clubbed feet, adactyly, syndactyly, or polydactyly, diaphragmatic hernia, and heart, lung, and urogenital anomalies). Milder magnesium deficiency ($^1/_{130}$ control intake) maintained throughout pregnancy resulted in resorption of half the implantation sites and malformation of the living young at term. In addition to their congenital anomalies, the surviving young were anemic and edematous. Surprisingly, despite the marked fetal damage caused by the deficiency during gestation, the pregnant rats showed only mild signs of magnesium deficiency despite sharp drops in their plasma magnesium levels. The severity of fetal damage produced in these studies was greater than in other studies; there might have been concomitant trace element deficiencies. Magnesium defi-

ciency ($^1/_{130}$ of control intake), comparable to that produced in the less severely depleted rats of Hurley *et al.* (1976), but produced by adding salt mixtures with only the magnesium contents differing, resulted in less severe damage (Dancis *et al.*, 1971; Cohlan *et al.*, 1970). When the magnesium-deficient diet was fed from the second day of gestation to term, only one of eight rats bore a litter; the remainder had evidence of resorption at implantation sites. When the magnesium-deficient diet was fed from ninth or tenth day to term, the magnesium-deficient rats all produced live litters (8.1/litter), but there were also 36 resorption sites among the 17 test rats. The control rats had no resorption sites and delivered 8.5 pups/litter. The pups born to deficient dams were small (2.6 ± 0.1 g, in comparison to control mean weight of 3.8 ± 0.3 g) and were weak and pale. There was consistent microcytic anemia; edema was prominent in the severely anemic fetuses. The control fetuses had higher plasma magnesium levels than did the fetuses of the magnesium-deficient rats, a finding suggesting that there is relatively little protection of the fetus against maternal magnesium deprivation. The mothers looked healthy at term, and although they had hypomagnesemia, their tissue magnesium levels were only slightly lowered. In contrast, the fetal tissues were markedly magnesium depleted (Table 3-3). There was little difference in placental magnesium in the control and deficient groups, but the placental calcium of the magnesium-deficient fetuses also had higher tissue calcium levels (105, as compared with 80.1 in control fetuses).

The less severe magnesium-depletion gestation study of Wang *et al.* (1971), which provided $^1/_{10}$ the control amount of magnesium to deficient rats, did not significantly reduce the number of offspring but markedly reduced their viability. Labor was prolonged in the depleted group, and 53 (36%) of the 146 offspring were stillborn. By the fifth day after birth, 82 more had died spontaneously or been eaten by their mothers; only 7.5% survived. There were no obvious abnormalities, other than small size and occasional swelling of extremities. The deficient mothers were normal in weight but had significantly lower-than-control levels of serum and bone magnesium. They also exhibited impaired lactation, and secreted milk significantly lower in magnesium than that of control rats. The survival of pups fed by the magnesium-deficient dams was poor.

Dancis *et al.* (1971) speculated that the higher placental and fetal calcium levels of the magnesium-deficient rats might have reflected increased fetal parathyroid activity.

TABLE 3-3. Magnesium Levels in Maternal and Fetal Tissues (From Magnesium-Deficient and Control Rats)[a]

	mEq/liter or kg ± SE	
	Magnesium-deficient	Control
Maternal plasma	0.33 ± 0.03	1.6 ± 0.04
Maternal bone	176.0 ± 12.1	213 ± 0.8
Maternal muscle	24 ± 0.5	23 ± 0.8
Fetal plasma	0.31 ± 0.02	2.4 ± 0.07
Fetus	8.9 ± 0.22	142 ± 0.39

[a] From data in Dancis *et al.* (1971).

3.2. *Perinatal Parathyroid Secretion: Interrelations with Magnesium and Calcium*

3.2.1. *Hyperparathyroidism of Pregnancy*

There is mounting evidence of magnesium insufficiency during pregnancy. Experimental acute magnesium deficiency has caused increased parathyroid secretion and even parathyroid hyperplasia (Larvor *et al.*, 1964a; Kukolj *et al.*, 1965; Gitelman *et al.*, 1965, 1968a,b; Lifshitz *et al.*, 1967; Sherwood *et al.*, 1970, 1972; Targovnik *et al.*, 1971). Thus, the possibility that magnesium deficiency is contributory to hyperparathroidism of pregnancy, which is common despite widespread supplementation with calcium and vitamin D at that time, should be considered.

Low normal or subnormal plasma phosphorus levels during pregnancy, which rise postpartum, have long been associated with maternal hyperparathyroidism (Mull and Bill, 1934, 1936; Mull 1936; Bodansky, 1939). This condition has been found so frequently as to be termed "physiologic" (Hamilton *et al.*, 1936; Cushard *et al.*, 1972). Rat studies have shown that pregnancy can cause significantly increased parathyroid volume (Opper and Thole, 1943). Significant maternal hyperparathyroidism has been demonstrated by immunoreactive parathyroid hormone (PTH) measurements, the levels of PTH being significantly higher during the third trimester and at delivery than in age-matched nonpregnant women and than in cord blood (Samaan *et al.*, 1973). Samaan *et al.* (1973) suggest that maternal hyperparathyroidism might be a response to the high fetal needs for calcium during the third trimester.

Despite hyperparathyroidism, serum calcium and magnesium levels both tend to be subnormal, especially during the third trimester of pregnancy (Watchorn and McCance, 1932; Mull and Bill, 1934; Mull, 1936; Bodansky, 1936; Kerr *et al.*, 1962; Newman, 1957; DeJorge, 1956b; Lim *et al.*, 1969b), which suggests that the gestational hyperparathyroidism can be secondary to hypocalcemia and/or to hypomagnesemia rather than physiological. Hyperparathyroidism has been found in mothers of infants with neonatal hypomagnesemia and hypocalcemia (J. A. Davis *et al.*, 1965; Ertel *et al.*, 1969; Monteleone *et al.*, 1975).

Ludwig (1962) reviewed the relationship of hyperparathyroidism to gestation and the products of conception, and found that there was a greatly increased incidence of complications of pregnancy and of fetal loss and infant morbidity among diagnosed hyperparathyroid women. Since asymptomatic hyperparathyroidism (with gestation-hypocalcemia) is common during even normal pregnancy and has been implicated in symptomatic infantile hypocalcemia, the possibility should be considered that there might be a common denominator that contributes to both. The importance of calcitonin secretion, both in the mother and the neonate, is gaining increasing recognition. The role of magnesium deficiency during gestation should also be considered, since it is involved in parathyroid dysfunction and in calcitonin secretion. Maternal abnormalities that predispose to neonatal convulsive hypomagnesemic hypocalcemia include maternal magnesium deficiency, which predisposes to maternal hyperparathyroidism and is apt to occur in: (1) adolescent or young mothers (whose own magnesium requirements may not be fully met); (2)

preeclamptic or eclamptic women; (3) women who have had several pregnancies in rapid succession, or with multiple births; (4) mothers with malabsorption; and (5) women with diabeties mellitus (Reviews: Tsang and Oh, 1970a; Tsang, 1972; Tsang and Steichen, 1975; Tsang *et al.*, 1977a,b). Intrinsic (pregestational) hyperparathyroidism, of course, falls into this category.

The possibility that magnesium deficiency of pregnancy might be contributory to both transitory and sustained maternal hyperparathyroidism (with low serum calcium levels) should be considered, and the response to magnesium adminstration investigated.

3.2.2. Fetal Parathyroid Activity and Phosphate, Calcium, and Magnesium Homeostasis

The fact that cord blood phosphate, magnesium, and calcium levels are usually higher than maternal levels (Bakwin and Bakwin, 1932; Finola *et al.*, 1937; Bruck and Weintraub, 1955; Delivoria-Papadopoulos, 1967; Samaan *et al.*, 1973; Bergman, 1974; David and Anast, 1974; Tsang *et al.*, 1973b, 1976b) suggests that fetal homeostasis of these elements is at least partially independent of maternal factors. Maternal hyperparathyroidism has long been speculated to be a direct or indirect cause of neonatal hypoparathyroidism, which contributes to hyperphosphatemia and secondary hypocalcemia and hypomagnesemia that are seen in the early days to weeks of life (Friderichsen, 1938, 1939; Van Arsdel, 1955; Hutchin and Kessner, 1964; Hartenstein and Gardner, 1966; Mizrahi *et al.*, 1968; Ertel *et al.*, 1969; Tsang *et al.*, 1973a). Severe enough experimental hyperparathyroidism in pregnant rats, however, to cause hypercalcemia and renal and myocardial damage in the mothers caused no more fetal hypercalcemia than was seen in control fetuses and caused no fetal soft tissue calcinosis (Krukowski and Lehr, 1961a,b; Lehr and Krukowski, 1961), suggesting that the placental barrier protected the fetus against maternal hyperparathyroidism. These investigators reviewed the literature at that time, and discussed the early experimental evidence that PTH does not penetrate the placental barrier, either from the maternal to the fetal circulation, or from the fetus to the mother. Earlier, Hoskins and Snyder (1933) showed that injection of PTH into the dog fetus *in utero* resulted in elevated fetal serum calcium levels not associated with a simultaneous rise in maternal plasma calcium levels. PTH injection into the pregnant dog raised maternal but not fetal calcium levels. An accidental finding during another study of the effect of hyperparathyroidism in dogs was obtained when one of the dogs was found to be pregnant (Cantarow *et al.*, 1938). The absence of damage to the fetuses, such as had been produced by PTH in the mother, was interpreted as indicating possible lack of passage of PTH through the placental barrier. When they confirmed these findings in their own controlled experiments with rats (Lehr and Krukowski, 1961; Krukowski and Lehr, 1963), they judged that since the placental membrane is at least three cell layers thick (Wislocki and Dempsey, 1955) even at the time of maximal placental permeability, large proteins such as PTH are unlikely to penetrate it. This hypothesis has been proved correct. Garel and Dumont (1972) have shown no demonstrable maternal–fetal or fetal–maternal crossover of tagged PTH in the rat. Injection of PTH to fetal rats has raised their

serum calcium levels, and influenced their serum magnesium and phosphate levels (Garel, 1971b; Garel and Barlet, 1974). The effect of PTH injections into the rat fetus suggests that it mobilizes bone calcium, as indicated by exposure of fetal rat bones to PTH (Raisz and Niemann, 1967, 1969). Garel and Barlet (1974) were unable to confirm earlier observations that PTH decreases fetal plasma phosphate (Garel and Geloso–Mayer, 1971), and speculated that mobilization of bone mineral by PTH should increase fetal plasma phosphate levels.

In contrast to the inability of maternal PTH to cross the placenta, calcium and magnesium are readily transferred across the placental barrier (MacDonald *et al.*, 1965). Their higher levels in fetal than in maternal blood suggest that there is active placental transport from maternal to fetal circulation (Economu-Mavrou and McCance, 1958; Aikawa and Burns, 1960; Cohlan *et al.*, 1970). An active placental transport mechanism involving calcium and magnesium-stimulated ATPase has been identified (Whitsett *et al.*, 1977a,b).

Inferential evidence has been obtained that modulation of increased or decreased fetal parathyroid activity protects the fetus against maternal hyper- or hypocalcemia and hyper- and hypophosphatemia, whether induced by dietary means; by maternal parathyroidectomy (Sinclair, 1942), high doses of PTH (Lehr and Krukowski, 1961; Krukowski and Lehr, 1963), or by hypervitaminosis D (Potvilege, 1962). The same should be true for protection against hyper- or hypomagnesemia. More recently there has been experimental proof that fetal parathyroids are functional. Garel and Geloso-Meyer (1971) demonstrated that thyro- or parathyroidectomy of pregnant rats causes fetal as well as maternal hypocalcemia, secondary fetal parathyroid hyperplasia, and resultant rises in the fetal plasma calcium levels. Ablation of the fetal parathyroids or injection of anti-PTH serum into the rat fetus (Garel, 1971a) has resulted in sustained fetal hypocalcemia. Production of fetal hypocalcemia by injection of the disodium salt of EDTA (which also chelates magnesium, although this was not measured) into sheep fetuses caused increased fetal PTH levels, but no change in the maternal PTH levels. In contrast, infusion of EDTA to normocalcemic ewes in late pregnancy caused a marked reduction in maternal plasma unchelated calcium and a doubling of maternal PTH levels, but no significant change in either of these parameters in the fetuses. Infusion of calcium to the pregnant ewes lowered their PTH levels but caused no change either in calcium or PTH levels of their fetuses (Care *et al.*, 1975). Studies in monkeys, however, have shown that fetal serum PTH was undetectable in the basal state and in response to EDTA-induced fetal hypocalcemia, although EDTA-induced maternal hypocalcemia caused 30–197% increases in maternal PTH values (A. R. Fleischman *et al.*, 1975). Whether the presumed simultaneously reduced serum magnesium levels interfered with release of PTH from the fetal glands requires investigation. Garel and Barlet (1976) have shown species differences in the parathyroid status at birth. Thus, there should be caution in applying experimental findings to human perinatal hormone/mineral interrelationships.

Much less work has been done on the fetal parathyroid response to low magnesium levels. Since fetuses of magnesium-deficient rodents show more damage than do the mothers, it seems likely that fetal parathyroid activity is less effective in protecting the fetus against hypomagnesemia than against hypocalcemia.

3.2.3. Hypoparathyroidism of Infancy

Hyperparathyroidism of pregnancy has long been blamed for hypoparathyroidism and low serum calcium/phosphorus ratios in the neonatal period (Friderichsen, 1939; Bakwin, 1939). The existence of neonatal tetany is considered a sensitive clue to maternal hyperparathyroidism. Hartenstein and Gardner (1966) reviewed the literature and found that there were seven reported families, including their own reports, in which neonatal tetany was associated with maternal parathyroid adenoma. Friderichsen (1939) was the first to report the association in an infant who developed infantile tetany at five months of age, and whose mother had osteitis fibrosa cystica secondary to her parathyroid adenoma. Brief reference was made to unusually severe signs of hypocalcemic neonatal tetany on the second day of life of two infants born to hyperparathyroid mothers (Talbot *et al.*, 1954). Maternal symptoms can well be absent in hyperparathyroid mothers whose premature or full-term infants present with severe tetany (Walton, 1954; Van Arsdel, 1955). A mother of eight children (four of whom had had hypocalcemic neonatal tetany developing at the 14th, 12th, 9th, and 2nd days) who had another pregnancy that aborted had asymptomatic parathyroid adenoma that was not diagnosed until her renal calcinosis was found a year and a half after the birth of her last child (Hutchin and Kessner, 1964). Conversely, infantile hypocalcemic tetany did not develop until one year of age in an infant, three months after cows' milk was substituted for breast milk, which had been provided by his mother who had had symptoms and signs of hyperparathyroidism (Bruce and Strong, 1955). Hypoparathyroidism was diagnosed in that child in his fourth year of life; a parathyroid adenoma was removed from the mother six years after he was born.

It was first suggested by Pincus and Gittleman (1925) that transient hypoparathyroidism might be at fault in a seven-week- old infant with nonrachitic tetany. Bakwin (1937) considered the susceptibility of neonatal infants to hyperphosphatemia and secondary hypocalcemic tetany to be a result of the phosphate load provided by cows' milk fed to infaats with end-organ unresponsiveness to PTH at birth. However, fetal plasma phosphorus levels are usually considerably higher than are maternal plasma levels (McCance and Widdowson, 1954, 1961), and even breast-fed infants who do not have a free supply of milk during the first 48 hours show a rise in serum inorganic phosphate after the first 24 hours (McCance and Widdowson, 1961). This rise has been attributed to the expenditure of tissue glycogen and protein to maintain life while the intake is minimal, an observation that has been supported by study of fasting newborn pigs (McCance and Widdowson, 1957). Before and at birth (cord blood) there are elevated fetal or infant plasma phosphorus levels that are associated with higher than maternal plasma levels of calcium and magnesium (Reviews: Smith, 1959; Bergman, 1974; Tsang *et al.*, 1976b).

3.2.3.1. Hypocalcemia of Infancy

A few hours after birth, infants commonly exhibit sharp drops in plasma calcium levels (Review: L. Bergman, 1974). Their phosphate levels tend to remain

high for days to weeks, especially those fed cows' milk. This is seen in normal full-term infants but is particularly marked in low-birth-weight infants, those that are born to diabetic mothers, or those that have been born after difficult deliveries and suffered birth hypoxia or later respiratory distress. It has been stressed that early neonatal hypocalcemia should be distinguished from that developing only after a week of life or later, which is related to the phosphate load of cows' milk. The foregoing section on neonatal and persistent infantile hypoparathyroidism [particularly with reference to the four siblings who developed the syndrome at 2–14 days (Hutchin and Kessner, 1964)] suggests that there might be a common denominator for both, and that the phosphate load precipitates the syndrome in less abnormal infants.

The greater prediliction for hypocalcemia and hyperphosphatemia among premature than full-term infants, and the rarity with which breast-fed infants develop these abnormalities within the first three weeks of life, were clearly depicted by Bruck and Weintraub (1955). Both groups had lower calcium levels after birth than they had had in their cord blood. Few of the premature hypocalcemic infants had tetanic symptoms; they more commonly presented with convulsions, hypersensitivity, rigidity, edema, vomiting, respiratory disturbances, and drowsiness. However, there were frequently no abnormal symptoms. The authors cautioned against considering asymptomatic hypocalcemia as "physiologic," since sudden transition from latent to manifest tetany is frequent. In the 1918 review of infantile tetany by Howland and Marriott, they reported four publications on the syndrome from 1815 through 1887. They were the first to observe that the syndrome could occur in the absence of rickets, and that it was far more common in cows'-milk-fed than in breast-fed infants. Dodd and Rapaport (1949), in their review, reported only sporadic cases from 1913. Among their own series of 33 infants with symptomatic neonatal hypocalcemia, 22 had convulsions, 28 had vomiting, 16 had edema (severe in 9), and 12 were cyanotic. Hemorrhagic manifestations included hematemesis (6 cases), melena (4), and hemoptysis or petechiae (2). Saville and Kretchmer (1960) commented on the rarity of reports of neonatal tetany until late in the 1930s, and its increasing frequency thereafter. They reviewed the evidence that a combination of cows' milk and vitamin D supplementation, together, were potent means of inducing infantile hypocalcemia and considered the high incidence in the literature among infants born after difficult labor or to diabetic mothers. They confirmed these observations in their series of 125 cases in a major medical center from 1940 to 1958. Only 33% were the products of normal full-term pregnancies and uneventful labor. Almost a tenth were born to diabetic mothers. Both low-birth-weight infants and those born to diabetic mothers, as well as other "sick" and hypocalcemic infants, have been shown to have subnormal parathyroid function (L. David and Anast, 1974; Samaan *et al.*, 1973; Tsang *et al.*, 1973b, 1975a, 1976a, 1977a; Bergman, 1974; Bergman *et al.*, 1974; David *et al.*, 1976, 1977).

It has been speculated that the hypoparathyroidism of infancy might be related to parathyroid immaturity (especially in premature or dysmature infants), to functional parathyroid deficiency, or to fetal hypercalcemia, possibly deriving from maternal hyperparathyroidism-induced hypercalcemia that might cause fetal PTH suppression, mediated by resultant fetal hypercalcemia (Reviews: Tsang *et al.*, 1973a, 1976a).

On the basis of the early experimental evidence as to fetal parathyroid competence, Lehr and Krukowski (1961b, 1963) commented that it is invalid to blame the neonatal rise in serum phosphate, with resultant drop in serum calcium, on the inability of functionally immature neonatal parathyroids to compensate for the loss of maternal PTH. They suggested that the difference between maternal and fetal serum calcium levels might reflect the higher pCO_2 in fetal blood, a deduction made on the basis of their observation that hypoxic fetuses (taken from dams after sacrifice) had markedly higher serum calcium levels than did fetuses without hypoxia (taken from living anesthetized dams) (Krukowski and Lehr, 1963). They proposed that the drop in serum calcium to normocalcemic levels immediately after birth might be mediated by initiation of respiration with blowing off of excessive CO_2. It is of interest, in this regard, that correction of neonatal acidosis by administration of bicarbonate in premature infants (Tsang and Oh, 1970a; Tsang *et al.*, 1976b), in infants with intrauterine growth retardation who often have asphyxia (Tsang *et al.*, 1975a), and in infants (often with respiratory distress) of diabetic mothers (Tsang *et al.*, 1974) results in further reduction in serum calcium, with production of continued hypoparathyroidism. These findings call to mind the hypothesis of Barzel (1971) that PTH function is influenced by the bicarbonate/carbonic acid buffer system. He has shown that hypoparathyroid patients have simultaneously elevated plasma phosphate and pCO_2 levels, with normal blood pH. However, the persistence of hypoparathyroidism, despite both hyperphosphatemia and hypocalcemia in infants whose elevated pCO_2 and acidosis have subsided, suggests that another mechanism can be operative. It is unlikely to be neonatal parathyroid immaturity; fetal parathyroid function has been shown to protect the fetus against experimental maternal aberrations in phosphate, calcium, and magnesium levels; and immunoreactive evidence of fetal PTH has also been obtained *(supra vide)*.

Nonetheless, low plasma PTH levels have been demonstrated in the first day or two of life (Tsang *et al.*, 1973b; Samaan *et al.*, 1973; L. David and Anast, 1974; Root *et al.*, 1974; Tsang *et al.*, 1975a), indicating failure of PTH secretion or release during the early neonatal period. Tsang *et al.* (1973b) have shown that PTH levels did not increase during the 24- to 48-hour period during which serum calcium levels fell. They found no relationship between serum PTH levels and total and ionized calcium in maternal, cord, and infant sera. Less gestationally mature infants had less increase in serum PTH during hypocalcemia than did the more mature infants. In contrast, David *et al.* (1976, 1977) showed that low-birth-weight infants had higher immunoreactive (i) PTH levels at birth than did normal adults, and that the iPTH levels increased earlier and were higher than in normal full-term infants (David and Anast, 1974; David *et al.*, 1977). These investigators commented on the difference between their findings and those of Tsang *et al.* (1973), whose study infants were more severely hypocalcemic than were those of David *et al.* (1977). Additionally, the infants in the French study (David *et al.*, 1977) were breast-fed; those in the American study (Tsang *et al.*, 1973b) were bottle-fed. Possibly the absence of hyperphosphatemia and hypomagnesemia in the French infants might reflect the difference in the feeding customs. It is conceivable that the rise in iPTH in premature rhesus monkeys as early as six hours after delivery (Fleischman *et al.*, 1975) might be similarly explained.

3.2.3.2. Magnesium Deficiency and Infantile Hypoparathyroidism

The evidence that magnesium deficiency during gestation and in the neonatal period can be correlated with parathyroid dysfunction suggests that magnesium deficiency might well be an important contributory factor to infantile hypoparathyroidism, failure of target organ response to PTH, and to hypocalcemia. Inadequate supply of magnesium to the fetus can result from insufficient maternal intake, abnormalities of pregnancy during which there is subnormal maternal magnesium or placental damage that interferes with transport of nutrients including magnesium to the fetus. High-risk infants, usually born to mothers with abnormalities of pregnancy, have a high incidence of transient or prolonged hypoparathyroidism with symptomatic neonatal hypocalcemia. Their magnesium deficiency is usually detected later, either as hypomagnesemia, often after calcemic agents have failed to control neuromuscular irritability, or by demonstration of high percentage retention of parenteral loads of magnesium.

Hypoparathyroidism was reported in two infant sisters (children of first cousins), in association with severe hypomagnesemia (0.5 and 0.4 mEq/liter, respectively) that was detected subsequent to treatment of their hypocalcemia with high doses of vitamin D (100,000 U/day) or dihydrotachysterol (Niklasson, 1970). Despite the calcemic agents, their serum calcium levels rarely reached normal or hypercalcemic levels. One exhibited mental retardation and emotional lability at 20 months of age. Convulsions were common in this family, a finding that suggests that there may have been a genetic abnormality in magnesium metabolism. The correlation of maternal magnesium deficit with maternal hyperparathyroidism, and with neonatal hypoparathyroidism and hypomagnesemic hypocalcemic tetany and convulsions, is inferential evidence that the infants reported by Niklasson (1970) are not likely to be unique. David and Anast (1974) showed immunoreactive PTH levels to be low during the first nine days of life in normal, "sick," and hypocalcemic infants. They found that depressed plasma magnesium levels (range = 0.97–1.25) were frequent (20%) in hypocalcemic infants. In normal newborn infants the range of plasma magnesium was 1.6–1.75 mEq/liter. These infants' hypomagnesemia was transient, usually reaching normal levels even when magnesium supplements were not given, or when the hypocalcemia was corrected by treatment with calcium. The rarer but more severe form of neonatal hypomagnesemic hypocalcemia associated with magnesium malabsorption must be treated wth large magnesium supplements for correction of parathyroid suppression.

However, an infant has been described with the same syndrome but with hyperparathyroidism (Monteleone *et al.*, 1975). The authors suggested that his seizures, which were intensified by calcium but responded to magnesium therapy, might have been causally related to hypomagnesemia secondary to his mother's hyperparathyroidism. They regretted that the PTH determination had been run after magnesium treatment had been started, thereby making it impossible to rule out the possibility of functional hypoparathyroidism immediately after birth. The infant's continued hypocalcemia and elevated PTH values suggested that he might have had target organ unresponsiveness to PTH, such as has been reported in magnesium-depleted older patients. They referred to the suggestion of L. Chase *et al.* (1974)

that hypomagnesemic patients with hypocalcemia might have impaired skeletal response to PTH, with decreased heteroionic exchange of magnesium at the bone surface, a hypothesis proposed also by Zimmet (1968), who cited Neuman and Neuman (1957) regarding the theory that cation exchange for calcium occurs predominantly at the hydration shell.

3.3. Calcitonin during Gestation; Interrelations with Magnesium and Calcium

3.3.1. Calcitonin during Pregnancy

Calcitonin (CT) levels are higher in maternal blood at time of delivery than they are in nonpregnant women (Samaan *et al.*, 1973a,b, 1975). Pregnant ewes have elevated CT levels during the last 40 days of gestation, both on a low- and high-calcium intake (Barlet, 1974; Barlet and Garel, 1974; Garel *et al.*, 1974, 1976; Garel and Barlet, 1975). Since the highest levels have been found in the ewes bearing triplets, there is support for the suggestion (Lewis *et al.*, 1971) that CT might function to protect the bones of pregnant or lactating females against excessive demineralization (by the increased PTH of pregnancy) to meet fetal calcium needs. The response to hypercalcemia in pregnant animals is increased CT secretion. Infusion of calcium salts has augmented the CT secretion of pregnant ewes (Garel *et al.*, 1973, 1974, 1976). Since pregnant women characteristically have hyperparathyroidism with hypocalcemia, as well as hypomagnesemia, the CT-stimulatory mechanism would appear not to be hypercalcemia. The hypocalcemia might reflect the response to CT secretion that spares the maternal skeleton. The mechanism by which CT secretion is increased in the presence of hypocalcemia, which (from the above studies) should decrease C-cell activity, remains unclear. Possibly, the simultaneously low magnesium levels during pregnancy play a role. For example, although magnesium-deficient rats show increased C-cell activity and release of CT in the presence of hypercalcemia (Stachura and Pearse, 1970), magnesium-deficient dogs with hypocalcemia also develop C-cell hyperplasia and evidence of increased secretory activity (Rojo-Ortega *et al.*, 1971, 1971/1973). Thus, during human pregnancy, when plasma levels of both calcium and magnesium are low, conflicting responses might be responsible for both hyperparathyroidism and hypercalcitoninemia.

3.3.2. Fetal Secretion of Calcitonin

Maternal CT has been shown not to cross the placental barrier in rats (Garel *et al.*, 1969, 1973, 1976) or in ewes (Garel *et al.*, 1974). Fetal thyroid tissue is able to secrete CT, which exerts a hypocalcemic effect (Garel *et al.*, 1968, Garel, 1969). That fetal C-cells can respond to hypercalcemia has been shown by Littledike *et al.* (1972) and Garel *et al.* (1973, 1974), who evoked significant increases in plasma CT in ovine, bovine, and porcine fetuses by acute elevations in fetal calcium levels.

Administration of exogenous CT to the rat fetus, late in gestation, lowers the plasma levels of all three elements; calcium, magnesium, and phosphorus (Garel *et al.*, 1968, 1969; Garel and Barlet, 1974). Samaan *et al.* (1975) attribute infantile hypocalcemia to elevated CT levels.

3.3.3. Neonatal Calcitonin

The level of immunoreactive CT (iCT) is significantly higher in the cord blood of full-term infants than in maternal blood at time of delivery following normal pregnancies (Samaan *et al.*, 1973a,b, 1975). By use of a method of determination that does not detect iCT in normal children and adults (150 pg/ml), David *et al.* (1977) found just detectable levels in cord blood of low-birth-weight infants, with a marked increase after 1–2 hours of age, and a peak almost 5-fold higher by 11 hours after birth. Similar findings were reported in infants of diabetic mothers (Bergman, 1974; Bergman *et al.*, 1974). Severalfold-higher plasma CT levels have also been detected in newborn lambs than in their mothers (Garel *et al.*, 1974), and the levels have risen in response to calcium per os (Garel *et al.* 1976) and in response to injection of cholecystokinin-pancreozymin (Barlet and Garel, 1976). Garel (1969) demonstrated that injection of CT into newborn rats produced a marked lowering of their plasma calcium levels. On the other hand, in subsequent work showing species differences in PTH/CT/Ca/Mg interrelationships in newborn ruminants, Garel and Barlet (1976) pointed out that the CT levels do not necessarily correlate with plasma calcium levels. Bergman (1974) postulates that high levels of growth hormone (i.e., in response to glucose infusion) at the time that CT levels are high increases the risk of neonatal hypocalcemia. Samaan *et al.* (1975) attribute infantile hypocalcemia to elevated CT levels.

The high blood levels of CT of neonates, and the preliminary evidence that CT secretion is increased in magnesium depletion (Stachura and Pearse, 1970; Rojo-Ortega *et al.*, 1971), as well as in the presence of high magnesium levels (Radde *et al.*, 1970; Care *et al.*, 1971; Littledike and Arnaud, 1971; S. P. Nielsen, 1971/1973, 1974; Barlet *et al.*, 1974), suggests that early and sustained infantile hypocalcemia might be a function of combined hypomagnesemia/hypoparathyroidism/increased CT secretion—all of which respond to moderate doses of magnesium. The possibility that perinatal magnesium deficiency might be a contributory or even a fundamental abnormality in the mineral and hormonal aberrations of the perinatal period has received little consideration.

3.4. Perinatal Hypervitaminosis D

3.4.1. Toxicity of Excess Vitamin D during Pregnancy

In the late 1930s, the decade that vitamin D supplementation became fairly commonplace, placental scarring and calcification were found to be more common in women supplemented with viosterol (vitamin D_2) than in those who were not

supplemented or who were given cod liver oil (vitamin D_3 + vitamin A) (Brehm, 1937). The same year, Finola *et al.* showed that viosterol (vitamin D_2, 250 U/day) given with calcium phosphate supplements caused little or no change in serum phosphorus levels as compared with the levels of those given the calcium salt alone, but several had serum calcium levels at or above 11 mg/100 ml (Fig. 3-1). Cord blood analyses showed a shift toward higher phosphorus levels and a higher incidence of hypercalcemia among infants of mothers given viosterol plus calcium phosphate than among those born to mothers on the calcium diphosphonate alone, although the averages were similar (Fig. 3-1). Both groups (Finola *et al.*, 1937; Brehm, 1937) expressed concern about the tendency toward intrauterine osteosclerosis in the infants of the vitamin-D-supplemented mothers, which was associated with narrowed and closed fontanels, a finding they considered contributory to longer, more difficult labors. Of greater concern to Brehm (1937) was the placental calcification, scarcely notable in those who had not had vitamin D supplementation, but so marked among several of the women given viosterol plus calcium as to interfere with placental separation. Three stillborn infants with severe renal calcification were born to that group of mothers. No note was taken in either of these studies of the maternal intake or levels of magnesium, but studies of customary magnesium intakes at about that time suggest that intakes might not have been optimal. These are preliminary observations that should be tested, a difficult undertaking with

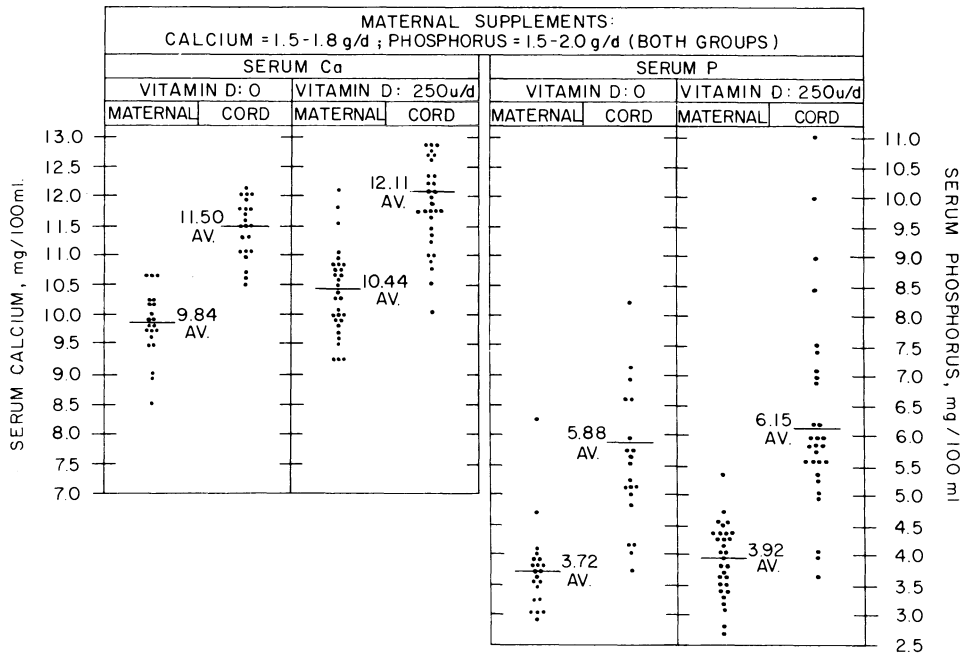

FIGURE 3-1. Serum calcium and phosphorus levels in maternal blood at delivery and in cord blood following maternal supplementation with calcium and phosphorus with and without vitamin D. (From MS Seelig: *Cardiovasc Med* 6:637–650, 1978.)

American women because milk in the United States is almost universally fortified with vitamin D_2 (400 units/quart) and calcium and vitamin supplements, providing 400 IU of vitamin D per tablet, are given to most pregnant women. This practice has been widespread since it was realized in the 1930s that failure to meet the demands for calcium, which increase manyfold during the last trimester, can cause maternal hypocalcemia (Cantarow *et al.*, 1938). The need for prenatal vitamin D supplementation was predicated on the observation of rickets of the newborn (Coons and Blunt, 1930).

Subsequent work suggests that this practice might not be uniformly beneficial. Low magnesium intakes, such as are common during pregnancy, in combination with calcemic agents, favor a high Ca/Mg ratio. Experimental studies show that high Ca/Mg and Na/K ratios increase arterial resistance (Review: Haddy and Seelig, 1976/1980. Whether the high Ca/Mg ratio of intake during pregnancy might contribute to toxemic hypertension must be explored. Furthermore, normal and abnormal vitamin D metabolites have widely differing potency and toxicity (Seelig and Mazlen, 1977). Whether subjection of foodstuffs, to which vitamin D has been added, to a variety of cooking processes might convert the antirachitic factor to more toxic derivatives has not been investigated. It is known, for example, that peroxidized cod liver oil and some of its fractions can damage the placenta, with resultant intravascular coagulation and eclampsia in rats (McKay, 1962; Kaunitz *et al.*, 1962, 1963; McKay and Goldenberg, 1963; McKay and Wong, 1962; McKay *et al.*, 1967). Also, administration of high doses of even untreated vitamin D_2 to rats has caused decreased placental volume, with atrophy and mucoprotein infiltration in the portion of the placenta composed of allantoic villi carrying fetal vessels (Potvliege, 1962). The fetal capillaries show degeneration of the endothelial cells, and the intervillous spaces collapse and become relatively bloodless. Calcium deposition occurs late in degenerated villi and in the walls and surrounding mesenchyma of large fetal vessels. Ornoy *et al.* (1968) has also shown that hypervitaminosis D in rats causes decreased placental volume. The young of the hypervitaminotic rats with placental pathology are small for gestational age, a finding similar to that seen in human infants born to eclamptic mothers or to others with abnormal placentas. Potvliege (1962) has found that there is also significant decrease in the volume of the parathyroids both in dams and fetuses, suggesting that the vitamin D might have caused hypercalcemia in both. The mothers had marked systemic calcinosis. The fetuses, however, showed neither vascular lesions nor excessive calcium deposition. In fact, pregnant rats that developed placental lesions (Ornoy *et al.*, 1968) had fetuses with defective bone formation. These investigators attribute the anomalous bone formation to damage to fetal osteogenic tissues induced by passage of excessive vitamin D_2 through the vitamin-impaired placenta. They speculate that vitamin-D-impaired placental function permits excessive vitamin D to reach the fetuses, and presume that fetal damage is caused by vitamin D_2 toxicity at the cellular level. W. Friedman and Roberts (1966) have shown that the blood levels of antirachitic substance are high both in rabbit mothers given toxic amounts of vitamin D_2 and their young, but the fetal damage produced resembles more that seen in human babies during the epidemic of infantile hypercalcemia during a time of excessive vitamin D prophylaxis of rickets (Reviews: Black, 1964; Seelig, 1969b) than that seen in the

rats. As with the rats, the does poisoned with vitamin D_2 had greater damage than did their young, but the offspring had cardiovascular lesions: supravalvular aortic stenosis (Coleman, 1965; Friedman and Roberts, 1966; Friedman, 1968), endocardial thickening (Coleman, 1965), and premature closure of the fontanels, osteosclerosis, and palatal abnormalities (Friedman and Mills, 1969). It seems likely that both vitamin D_3 and its 25-hydroxy-derivative cross the placental barrier from mother to fetus in the rat (Haddad *et al.*, 1971). Judging from comparable 25-OH-D_3 levels in maternal and cord blood, placental transport probably also takes place in humans (Hillman and Haddad, 1974; Belton *et al.*, 1977). The observation that levels of 25-OH-D_3 are lower in newborn rabbits with supravalvular aortic changes, born of does with hypervitaminosis D than they are in controls (Mehlhorn *et al.*, 1977) suggests that administration of toxic amounts of vitamin D might result in its abnormal metabolism. It can be speculated that, as the enzymes involved in normal vitamin D metabolism are overloaded, abnormal degradation products can be produced. Whether there are such abnormal products, and whether they are more toxic than the normal metabolites should be investigated.

Unfortunately, although the enzyme systems involved in hepatic and renal hydroxylation of vitamin D are magnesium dependent, magnesium levels have not been determined in the studies of vitamin D toxicity in pregnancy, nor in the damaged young. Since administration of high doses of magnesium is protective against vitamin D toxicity and magnesium deficiency intensifies the damage produced, the interrelationships of vitamin D and magnesium during pregnancy should be studied. Does magnesium deficiency increase the risk of vitamin D toxicity, and if so, to what extent? This is a cogent point, since the average American woman probably ingests considerably more than optimum quantities of vitamin D from fortified milk and other foods, as well as from prenatal supplements. Her intake of magnesium is likely to be marginal, at best, and is likely to be significantly low. Can magnesium supplements during pregnancy protect against vitamin D toxicity, and to what extent? This question might be relevant to protection against eclampsia, damaged placenta, and intrauterine growth retardation, as well as against fetal abnormalities—from bone to renal to cardiovascular anomalies—such as have been seen in experimental vitamin D toxicity during pregnancy, and some of which have been related to experimental magnesium deficiency itself. The nature of the fetal abnormalities caused by experimental hypervitaminosis D during gestation seems not be a function of the vitamin D alone, but to other components of the diet in ways that have not yet been clearly defined. The early study by Nicholas and Kuhn (1932) showed that their control pregnant rats given a complete diet that included fresh green vegetables and fruits, butter, yeast, and cod liver oil (a diet that was undoubtedly rich in magnesium, trace elements, and the B vitamins, as well as in vitamins A and D_3) had uniformly successful gestations. To explore the influence of viosterol, calcium, and phosphorus, diets were prepared that lacked the above ingredients, and that provided adequate calcium and phosphorus and that were supplemented with or free of vitamin D_2 (viosterol). Because of the absence of the additional nutrients in the "basic" experimental diet, the less successful gestations of the rats on that diet when viosterol was added reflects more than the influence of the vitamin D_2. It is interesting, however, that the rats receiving the basic diet, adquate in calcium and phosphorus, did not tolerate the viosterol as well as did

those on the diet that was deficient in calcium and phosphorus. When viosterol was given throughout pregnancy, none of the rats getting calcium and phosphorus delivered young; when given viosterol only during the last 14 days, two in ten rats came to term. One of the five calcium and phosphorus-deficient rats given viosterol throughout gestation came to term; five of seven given viosterol the last 10 to 14 days delivered young. Other than size and calcium and phosphorus ash content of the pups, no data were given as to their status at birth. The pups born to viosterol-supplemented dams, whether or not they had had calcium or phosphorus deficiency, were larger and had higher calcium and phosphorus contents than did control pups or those on the basic diet.

3.5. Summary of Maternal Factors That Might Contribute to Infantile Magnesium Abnormalities: Morbidity and Mortality

Abnormalities in magnesium metabolism during pregnancy (as a result of, or a contributory factor in, vitamin D, PTH, CT, calcium, and phosphorus imbalances) have been shown to influence profoundly the success of gestation and the status of the newborn infant. Forfar (1976) has listed some of the mechanisms that can contribute to disturbances in mineral metabolism in the perinatal period. He cited:

1. Inherent (genetic) defects in the parents transmitted to the offspring.
2. Congenital absence or hypoplasia of the parathyroids.
3. Disturbance of the maternal (intrauterine) mineral status with reciprocal fetal disturbances.
4. Nutritional deficiency.
5. Placental insufficiency and IUGR.
6. Prematurity.
7. Perinatal asphyxia and birth injury.
8. Excess phosphorus in infant feedings.
9. Eclampsia.

This listing is useful as a summation of many factors that have been presented in this section, interactions among which are frequent. Some additional data in several of the categories might further explicate some of the interrelationships, and shed some light on metabolic aberrations that might be contributory to clinicopathologic findings in the perinatal period.

3.5.1. Genetic Hypoparathyroidism

Absence or hypoplasia of the parathyroids is usually characterized by symptoms and signs of hypocalcemia. Although often also present, hypomagnesemia is less frequently sought and detected. This disorder is often associated with other endocrinologic abnormalities, including that of the thymus, and by lymphopenia and other immunologic deficienices. This constellation of abnormalities is suggestive that magnesium deficiency might be an underlying factor, since it causes not

only parathyroid dysfunction (Review: Nusynowitz *et al.* 1976) but also has been implicated in thymic hyperplasic and immunologic abnormalities (Reviews: Hass *et al.*, 1976/1980; Larvor 1976/1980).

3.5.2. Genetic Hyperparathyroidism

Pregnant women with hyperparathyroidism generally have infants with at least transitory hypoparathyroidism (*supra vide*). However, familial hyperparathyroidism has been implicated in infants with laboratory or autopsy evidence of hyperparathyroidism. Hillman *et al.* (1964) reported two siblings with marked parathyroid hyperplasia, who were born to consanguinous parents. The first was detected at autopsy, in association with metastatic calcification and osteoporosis. The second was verified at surgery for subtotal parathyroidectomy. Goldbloom *et al.* (1972) encountered a second pair of siblings with hyperparathyroidism, with all of the typical characteristics: bone demineralization (with signs of rickets), elevated serum calcium and magnesium, and hypophosphatemia. Both survived subtotal parathyroidectomy: the first at 30 months of age, and the second after the first week of life. Their literature review uncovered nine additional cases in seven families. Not included in their list were two infants who had hypocalcemia and hyperphosphatemia, such as are seen with infantile hypoparathyroidism, but who were found to have parathyroid hypertrophy at autopsy (D. H. Andersen and Schlesinger, 1942). Since these infants had arterial calcification, no early rickets but osteitis fibrosis at the time of death at four months, it is possible that their pseudohypoparathyroidism might have been secondary to magnesium deficiency. The data from the infant reported by Monteleone *et al.* (1975) supports this speculation. He developed seizures on the ninth day of life and had slightly low serum calcium (7 mg/100 ml) and hyperphosphatemia. After intravenous calcium (which only partially controlled the seizures) his serum magnesium level was 0.8 mg/100 ml. Treatment with parenteral magnesium was more effective. A blood specimen taken three days later was found to have elevated iPTH levels. Thus, pseudohypoparathyroidism is another abnormality that might be related to magnesium depletion.

3.5.3. Reciprocal Maternal and Fetal Mineral Status

The maternal and intrauterine magnesium and calcium status has been considered in this section, as influenced by PTH, CT, vitamin D, and by impaired placental function, as well as in Chapter 2. The special role of excessive phosphate and vitamin D during infancy is considered in Section 4.3. The risk of prenatal vitamin D deficiency, as a cause of neonatal rickets, persists in groups with high vitamin D requirements. Whether the vitamin D refractoriness of magnesium deficiency might prove germane to the problem in pregnancy requires investigation.

3.5.4. Maternal Age and Parity: Diabetes Mellitus

It has been pointed out that very young (adolescent) mothers—who constitute many of the primaparous mothers with complications of pregnancy and premature or low-birth-weight infants—are at particular risk of poor dietary intake, including

magnesium, the average intake of which is low during pregnancy. Young multiparous mothers, particularly those whose pregnancies have been frequent, and mothers of twins or greater multiple births, are also especially prone to magnesium depletion. Mothers with diabetes mellitus (a condition noted to be associated with hypomagnesemia even in the absence of pregnancy) have also delivered infants with subnormal magnesium levels. It has also been found that mothers of infants with neonatal hypocalcemic convulsions (such as have been shown to be associated with hypomagnesemia) are often significantly older, of higher parity, and of lower social class than controls (S. Roberts *et al.*, 1973). Such mothers might be presumed to have been on suboptimal magnesium intakes, and to have been depleting their own magnesium stores with each successive pregnancy.

3.5.5. Eclampsia

Of particular importance are the low magnesium levels and high percentage retentions of pharmacologic doses of magnesium given to preeclamptic and elcamptic women. As has been discussed, the high fetal mortality of infants of eclamptic women is being increasingly attributed to placental damage, with resultant intrauterine malnutrition and hypoxia. Brash (1949) reviewed the literature to that time and evaluated 120 full-term live-born infants of toxemic mothers as compared with the same number of infants born after normal pregnancies. The incidence of abnormal lethargy, sometimes with edema or convulsions for days after birth was 11:1 in infants of toxemic mothers versus those born of normal mothers. Stillbirths and neonatal deaths occurred in 10.7 and 5.2%, respectively, of the infants born after eclampsia, and in 3.9 and 2.9% of those born after normal pregnancies. The observation that fetal salvage is improved in eclamptic women treated with magnesium sulfate alone, as compared with that of those given other antihypertensive and anticonvulsant medications (Zuspan and Ward, 1965; Zuspan, 1969) is further suggestive evidence of the importance of magnesium for both mother and infant.

4
Magnesium Status in Infancy

The magnesium levels at birth (indicated by cord levels) reflect the fetal response to maternal conditions during gestation: systemic and placental, and the ease or difficulty of delivery with resultant normal or hypoxic state of the newborn infant. Conditions that lead to neonatal hypermagnesemia might mask an underlying magnesium deficiency. Hypermagnesemia might result from administration of pharmacologic doses of magnesium to the mother shortly before delivery for management of toxemia of pregnancy, or from egress of magnesium from the tissues of infants subjected to anoxia, acidosis, or surgery. Exchange transfusions with citrated blood profoundly affect magnesium as well as calcium homeostasis. Levels during the first week of life reflect the infant's adjustment to independent life in the absence of immediate maternal blood-borne factors, and are affected by the nature of milk and supplements provided. The nature of feeding also influences levels later in infancy. Metabolic abnormalities that interfere with magnesium absorption or retention, although not common, have produced severe mineral imbalances that have focused pediatricians' attention on magnesium. More common conditions, such as severe diarrhea and intestinal malabsorption syndromes, which also cause hypomagnesemia, have further stimulated the pediatrician to be alert to magnesium loss. This section calls attention to the conditions and mechanisms that make infants susceptible to magnesium deficiency and presents speculations as to possible late, as well as overt, immediate sequellae.

4.1. Infantile Magnesium Deficiency: A Factor in Hypocalcemic Tetany, Seizures, and Respiratory Distress

It has long been recognized that neonatal hypocalcemia causes neuromuscular irritability and frank seizures. That the hypocalcemia is secondary to hypomagnesemia in many instances is now clearly established: as a factor in neonatal hypoparathyroidism, in vitamin-D-resistant rickets, and in genetic magnesium malabsorption. Treatment of infantile hypocalcemia with calcemic agents, which can

intensify any preexisting magnesium insufficiency, has been shown to cause severe hypomagnesemia and intensification of the clinical manifestations that predicated their use. It is possible that such treatment can be a contributory factor in subsequent renal tubular wasting of magnesium, which can result from intraluminal renal tubular calculi.

Acute magnesium deficiency of infancy severe enough to cause tetany or convulsions, usually in association with hypocalcemia and occasionally with hypercalcemia, was first reported in 1921 by Denis and Talbot. They analyzed plasma calcium levels in 116 hospitalized infants and young children and reported magnesium levels in 38 of those patients. Of the 24 who had hypomagnesemia, six had seizures; two of the older children, four and five years of age, who had been diagnosed as having epilepsy or petit mal had hypocalcemia as well as hypomagnesemia. Three more had tetany; one of those died with laryngospasm at seven months. There were four additional young children (seven months to three years of age) with convulsions, and one with tetany, who had not had their plasma magnesium levels measured. One with microcephaly and mental retardation and one with mental retardation alone had plasma calcium levels of 9.2 and 9.7 mg/100 ml at seven months and two years, respectively. (Another baby with microcephaly and mental retardation, who had plasma calcium of 13.5 mg/100 ml at one year of age, may be the first recorded instance of the infantile hypercalcemia syndrome.) The remaining three babies with seizures or tetany had plasma calcium levels between 5.5 and 8.2 mg/100 ml.

Until the past 15 years, few papers evaluated the magnesium status of infants with abnormalities that later investigations suggest might well have been related to perinatal magnesium deficiency. The infants with tetanic or convulsive signs of hypocalcemia, which were associated with maternal hyperparathyroidism and became worse following treatment with calcemic agents, might have had contributory magnesium deficiency. So, also, might those born after complicated pregnancies or difficult deliveries, which has been shown to predispose to infantile convulsions (S. Wallace, 1972).

The role of hypomagnesemia in infantile convulsions has gained increasing recognition since J. A. Davis *et al.* (1965) reported an infant with hypomagnesemic neonatal fits, born to a mother with chronic malabsorption, and Paunier *et al.* (1965, 1968b) identified isolated magnesium malabsorption of infancy as a newly recognized genetic disorder. This condition is associated with hypocalcemic tetany and convulsions that require high doses of magnesium for correction. Use of calcium infusions or calcemic agents, such as high doses of vitamin D or parathyroid hormone, can intensify the neuromuscular irritability, and often do not even correct the hypocalcemia. However, far more infants than those unusual children with magnesium malabsorption are subject to hypomagnesemia. For example, the same year that Paunier *et al.* (1965) published their preliminary report, Davis *et al.* (1965) reported an infant boy with convulsions that started on the eighth day of life, and who had hypocalcemia, hypomagnesemia, and hypoglycemia. His intermittent fits became continuous following glucose and calcium infusions that raised his blood glucose to normal but exerted no influence on the hypocalcemia (Fig. 4-1). The seizures stopped within 30 seconds of intravenous administration of 2.5 mEq of

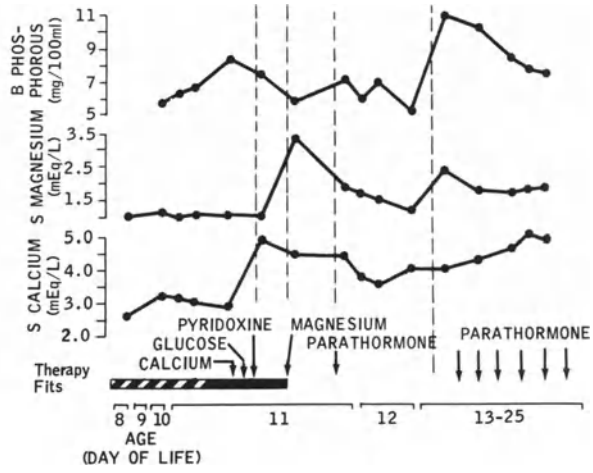

FIGURE 4-1. Response of neonatal hypocalcemia to magnesium, calcium, and parathyroid hormone. (From JA Davis *et al.*: *Arch Dis Childh* 40:286–290, 1965.)

magnesium, and his strongly positive Chvostek's sign became negative. The authors considered maternal hyperparathyroidism (secondary to long-term intestinal malabsorption) to have resulted in transitory suppression of her baby's parathyroid function. He responded to PTH by increased clearance of phosphate and decreased calcium and magnesium excretion, despite which his serum magnesium again declined, but without recurrence of convulsions.

Following the detailed study of the second reported (male) infant with magnesium malabsorption (Salet *et al.*, 1966), and the suggestion that the disease might be hereditary in a third boy (M. Friedman *et al.*, 1967), two more male infants developed convulsive hypomagnesemic hypocalcemia. One was born to a mother with poorly controlled diabetes mellitus (Clarke and Carré, 1967) and thus might have had intrauterine magnesium deficiency. The other was born to a mother with hypophosphatemia, who had received Dilantin therapy for many years (Dooling and Stern, 1967), and thus might have been magnesium deficient before and after birth. The infant born to the diabetic mother (Clarke and Carré, 1967) had had a low Apgar score at one minute and developed respiratory distress a few hours after birth. He had clonic convulsive movements on day 13, which responded to addition of calcium chloride to his formula until day 32, when his convulsions recurred. They intensified on addition of AT-10 (a dihydrotachysterol), high dosage vitamin D, and intravenous calcium gluconate, which did not increase his serum calcium levels. His serum magnesium was then measured and found to be 0.6 mEq/liter. A single intramuscular injection of magnesium (1 ml 50% $MgSO_4$) resulted in cessation of convulsive movements a few minutes after the injection; the improvement persisted thereafter and no further magnesium supplements were given. The infant who had received the exchange transfusion (Dooling and Stern, 1967) showed continuation of irritability, tremulousness, and convulsions, after a focal seizure on day 6, that persisted (during calcium therapy) until his hypomagnesemia was detected and cor-

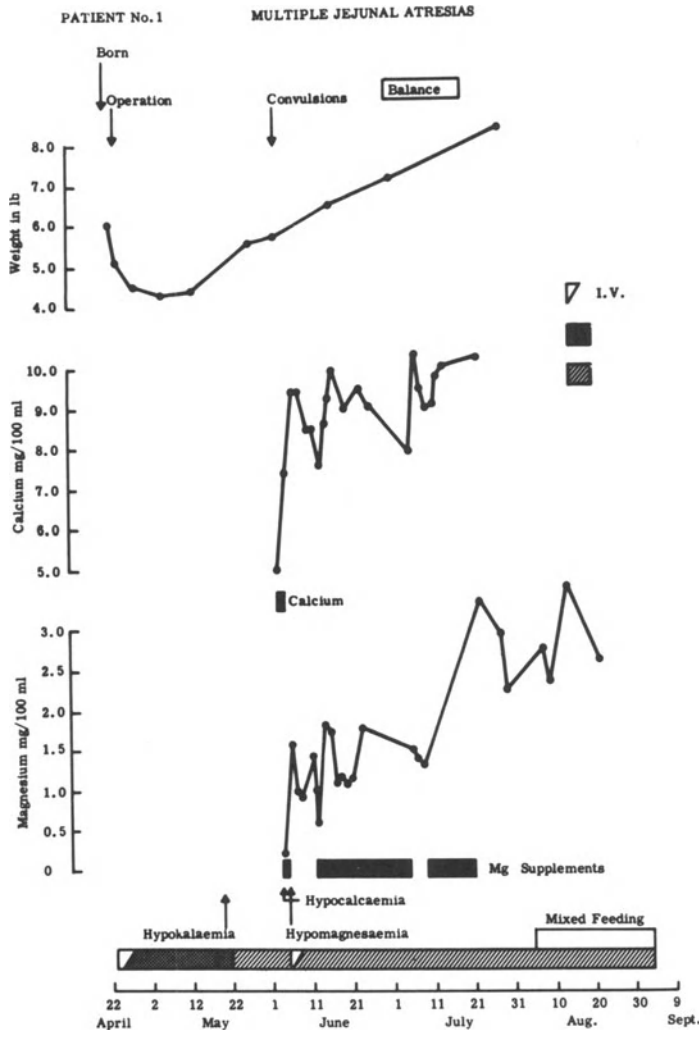

FIGURE 4-2. Postoperative serum Ca and Mg in infant; rise and fall of Ca corresponding to oral administration of Mg. (From JD Atwell: *J Pediat Surg* 1:427–440, 1966.)

rected. Atwell (1966) presented detailed studies of three infant boys who developed hypomagnesemia and hypocalcemia and were unresponsive to calcium infusions after neonatal gastrointestinal surgery, but who responded to magnesium (Fig. 4-2).

The clustering of reports of neonatal infants, whose hypocalcemic convulsions could be directly attributed to magnesium deficiencies of different etiologies led to an editorial (*Canad MAJ*, 97:868, 1967) that pointed out that hypomagnesemia is more likely to be a crucial medical problem than a chance occurrence. Stressed was the need for ready availability of facilities to monitor serum magnesium levels, certainly in convulsing infants, and also in other conditions associated with hypomagnesemia, including hypervitaminosis D and use of diuretics, and in the protein-cal-

orie-malnutrition syndrome. Because of sudden death occurring in infants receiving exchange transfusions, and the evidence that citrated blood lowers blood magnesium levels (Bajpai *et al.*, 1967a,b), the editor also called for determinations of magnesium levels in such infants, or preferably using heparinized rather than citrated blood for exchange transfusions. Neonatal infants requiring major surgery, who also generally are transfused, are also at risk of hypomagnesemia (Atwell, 1966; Jalbert *et al.*, 1969).

There have been many published case reports and reviews published since, in which hypomagnesemia is the common denominator in several otherwise unrelated conditions characterized by neonatal and later infantile tremors, tetany, and convulsions. Most are associated with hypocalcemia, but several show a poor correlation with plasma calcium levels. Whether hypocalcemic tetany or convulsions associated with normal magnesium levels in the serum (which can rapidly attain normal levels despite tissue deficit) is another manifestation of a related metabolic disorder requires further study.

4.1.1. Magnesium Deficiency in Metabolic Convulsions of Otherwise Normal Newborn Infants

The group in Scotland that considers disturbed magnesium metabolism to play a significant role in neonatal convulsions in otherwise normal infants (Forfar *et al.*, 1971/1973; J. K. Brown *et al.*, 1972; Cockburn *et al.*, 1973; Forfar, 1976; T. Turner *et al.*, 1977) observes that this syndrome occurs in bottle-fed, but generally not in breast-fed, infants. They have presented evidence that both plasma and cerebrospinal fluid (CSF) levels of magnesium and calcium are lower in convulsing than in normal infants; the CSF phosphorus level of convulsing infants is normal despite hyperphosphatemia. The babies with convulsions are described as classically "jittery." They found the syndrome to be severe in 35% and lesser in degree more frequently. Among 75 consecutive newborn infants with convulsions considered due primarily to disordered mineral metabolism, seen over a two-year period, subnormal calcium levels (more than 2 S.D. below the mean) were seen in 92%, subnormal magnesium levels in 52%, high phosphorus levels in 67%, and combinations of biochemical disturbances in 80% (Fig. 4-3). Hypocalcemia was associated with hyperphosphatemia in about 60% and with hypomagnesemia in about half of the cases. Hypomagnesemia without hypocalcemia was seen in 7%, almost half of whom also had normal phosphorus levels. Convulsions considered due primarily to brain damage (in 60 additional infants) often also exhibited mineral metabolism derangement, predominantly hypocalcemia and hyperphosphatemia (J. K. Brown *et al.*, 1972). Infants fed evaporated milk formulas had low magnesium and high phosphorus levels, comparable with levels of convulsing infants in 68 and 80% of the controls. In an evaluation of clinical and chemical relationships in neonatal convulsions, the group (J. K. Brown *et al.*, 1972) commented that they had encountered convulsions in 1.4% of live-born infants. Most of those classified as due to brain damage occurred in the first three days of life; most of those considered metabolic in origin occurred from the fourth day on (Fig. 4-4). They noted that the proportion of metabolic to brain-damage convulsions seems to have risen markedly

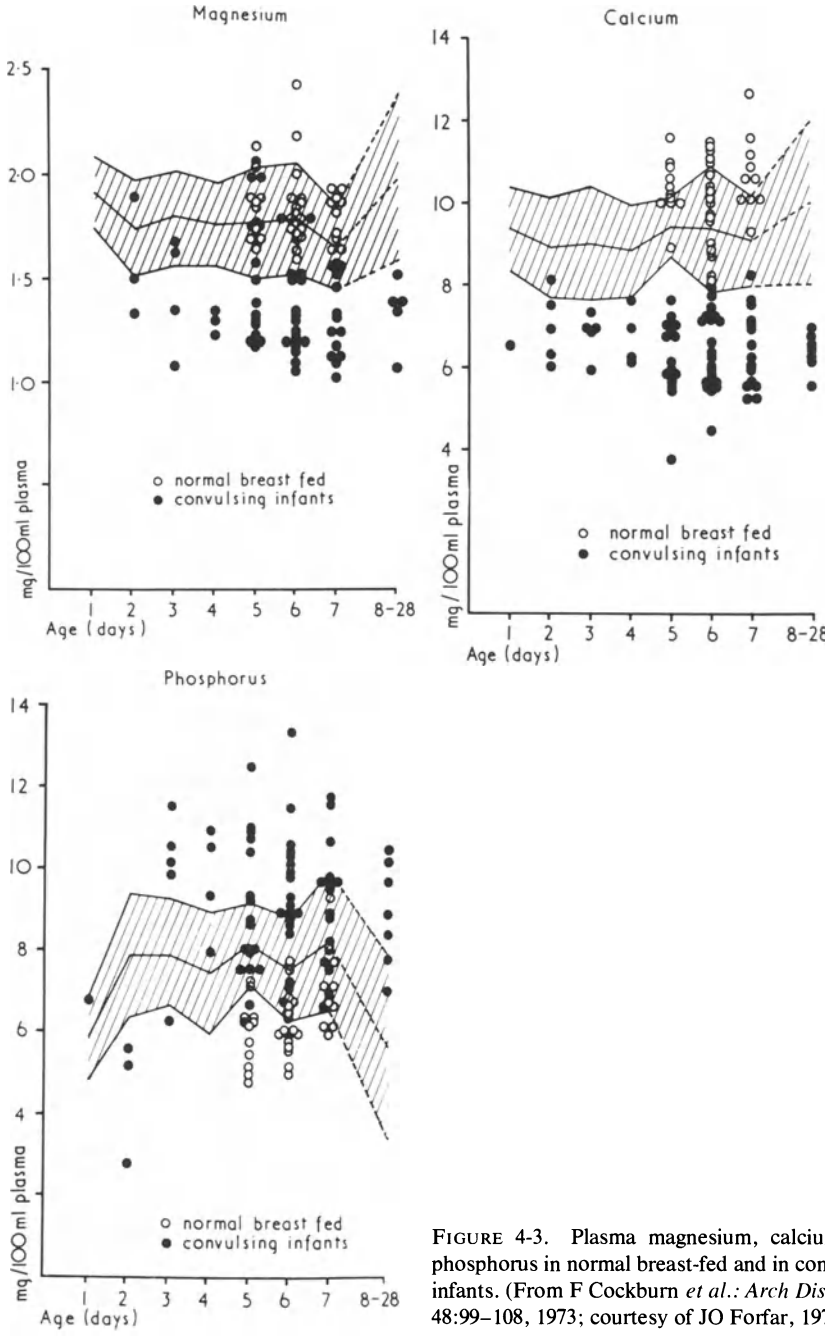

FIGURE 4-3. Plasma magnesium, calcium, and phosphorus in normal breast-fed and in convulsing infants. (From F Cockburn *et al.: Arch Dis Childh* 48:99–108, 1973; courtesy of JO Forfar, 1978.)

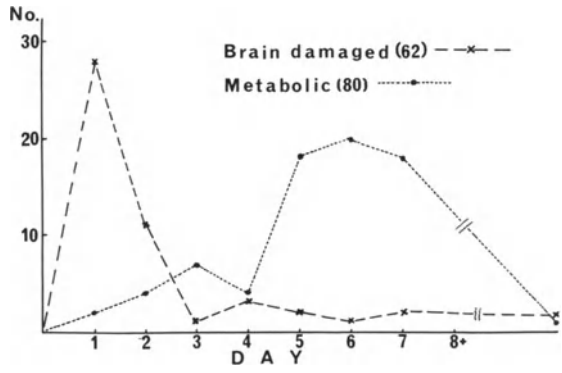

FIGURE 4-4. Neonatal convulsions (142). (Courtesy of J Forfar, 1978.)

in reports published since 1969, as compared with reports published between 1954 and 1960, during which time brain-damage-induced convulsions were predominant. Since metabolic convulsions are more amenable to correction, this is an important point in terms of management of convulsing infants.

Wong and Teh (1968) had earlier reported hypomagnesemia without hypocalcemia in five otherwise normal infants, during the week after birth. (This was part of a study of 40 babies and young children with convulsions, tremors, or muscular twitchings, 13 of whom had hypomagnesemia alone, and 27 of whom also had hypocalcemia). When symptoms were present, both total and ultrafiltrable mean levels of magnesium were significantly lower than in controls ($p = < 0.001$). The major decrease was in the ultrafiltrable moiety. Keen (1969), like Forfar and his colleagues (*supra vide*) called attention to the increasing incidence of infantile convulsions of metabolic origin in England. Of 100 infants with seizures in the first 4 weeks of life, 36 had hypocalcemia, with peaks of incidence in the first 48 hours and between the 4th and 10th days of life. Only toward the end of this 23-month study were magnesium levels determined. Details of the inconstant association of hypomagnesemia with hypocalcemia were not given, but the investigator considered the response of refractory hypocalcemic fits to magnesium (Davis *et al.*, 1965) as suggestive of its importance in this syndrome. He, too, commented on the disproportionate distribution of convulsions among bottle-fed as compared with breast-fed infants. Harvey *et al.* (1970) also showed that the mean magnesium level was lower in bottle-fed than breast-fed infants by the seventh day of life, and that among those with convulsions the mean was even lower. In this series, even many of the nonconvulsing infants had hypomagnesemia and hypocalcemia. This recalls Bruck and Weintraub's (1955) admonition that asymptomatic hypocalcemia should not be considered "physiologic," since transition from latent to manifest tetany is frequent and can occur unexpectedly. The same is likely to be true for hypomagnesemia. Furthermore, because of the evidence that prolonged chronic magnesium deficiency can contribute to cardiovascular, renal, and bone abnormalities, overt symptomatology may not be the major risk.

The infant reported by Vainsel *et al.* (1970) might be an example of delayed as

well as acute complications of magnesium deficiency of infancy. Although this infant had not had his severe hypomagnesemia (0.4–0.7 mEq/liter) detected until three days before he died at five and a half months, there is strong inferential evidence that magnesium deficiency was likely to have played a contributory role. He was the ninth child of a woman who had been treated for tuberculosis, and thus was probably magnesium depleted. [High parity contributes to the magnesium drain on the mother, and aminoglycoside antibiotics are magnesium wasters (Vanasin *et al.*, 1972).] Five of her seven sons had had seizures; three died. Two, counting the propositus, whose hypomagnesemia had been identified late (after massive calcemic therapy), had arterial calcinosis. That infant also had renal and myocardial calcinosis.

The frequency of low magnesium levels among infants with symtomatic hypocalcemia was noted by the investigators cited above, and in subsequent studies. Stern and Harpur (1971/1973) briefly reported six newborn infants whose hypocalcemia was clearly secondary to their hypomagnesemia. Radde *et al.* (1972) commented that symptoms and signs attributable to low ionized calcium levels were found only in infants who had low plasma levels also of magnesium. Tsang (1972), who reviewed in detail the factors contributing to neonatal magnesium disturbances, also commented on the concomitant hypocalcemia, and *vice versa*. Subsequent work from his group has elucidated the infants at greatest risk of the combined divalent cation deficiencies (Tsang *et al.*, 1973, 1974, 1976, 1977a,b; Tsang and Brown, 1975, 1977). David and Anast (1974) found that plasma magnesium levels were significantly lower in hypocalcemic than in normal or sick neonates.

Most of the infants described in this section were newborn. Convulsions and tetany associated with hypomagnesemia have also been reported in older infants and young children. Febrile convulsions are frequently associated with lower than normal serum magnesium levels, often without hypocalcemia (Chhaparwal *et al.*, 1971). A "meningo-encephalitic, or tremor" syndrome in Indian children has also been associated with hypomagnesemia in infants of 6–24 months of age, who have evidence of mental retardation and malnutrition (Chhaparwal *et al.*, 1971/1973). Severe magnesium deficiency also occurs during repair of protein calorie malnutrition (see pp. 122–128).

4.1.2. Low-Birth-Weight Infants

Lower cord blood magnesium levels have been reported in low-birth-weight infants than in full-term infants (Breton *et al.*, 1960; Review: Ferlazzo and Lombardo, 1971). When the low birth weight is due to prematurity, the low cord blood levels can be attributed to the subnormal accumulation of minerals in the final weeks of gestation. Widdowson and Dickerson (1962), who have tabulated the mineral contents of 1.5 kg, 2.5 kg, and full-term babies, have shown that the magnesium content of the more immature or smaller babies is only 42% that of normal size infants, while that of 2.5-kg infants is 76% that of the normal full-term baby. In regard to the tendency toward hypocalcemia of premature infants, the 1.5- and 2.5-kg infants have 36% and 68% the calcium contents, respectively, of full-term babies. This study did not differentiate between immature infants and those that are small for gestational age (SGA) as a result of intrauterine growth retardation (IUGR).

The hypocalcemia and hypomagnesemia of low-birth-weight infants can reflect inadequate stores accumulated before birth, in addition to postnatal problems in homeostasis. Their hyperphosphatemia can derive from tissue breakdown and be aggravated by inappropriate dietary intakes, functional immaturity, and hormonal imbalances. The hyperphosphatemia associated with hypocalcemia and hypomagnesemia that is found in full-term infants fed cows' milk rather than breast milk and that is aggravated by vitamin D is further discussed on pp. 105–108.

Renal tubular immaturity has been proposed as an explanation of the inability of the neonate to eliminate excess phosphate, whether endogenous or exogenous, that is associated with persistent hypocalcemia and hypomagnesemia. Rubin *et al.* (1949) showed that aspects of renal function mature at different rates, usually reaching adult values during the second year of life. Dean and McCance (1948) and L. Gardner *et al.* (1950) reported that renal tubular immaturity was responsible for the low phosphate clearance that they reported in neonatal infants. This fits the experimental evidence suggesting absence of fetal phosphaturic response to exogenous PTH (Garel and Barlet, 1974). Tsang *et al.* (1973b) found that phosphorus excretion increased in premature infants over their first three days of life, whether or not PTH was given. Their fractional tubular reabsorption fell and there was no significant difference in phosphorus excretion or reabsorption between the PTH-treated and nontreated infants.

The theory that transient hypoparathyroidism of infancy is a result of parathyroid immaturity has been discussed earlier. If valid, this theory is even more applicable to low-birth-weight infants and might explain their subnormal PTH response to neonatal hypocalcemia. Also suggested frequently is the possibility that fetal hypercalcemia, possibly deriving from maternal hyperparathyroidism-induced hypercalcemia, might cause fetal PTH suppression, mediated by resultant fetal hypercalcemia (Review: Tsang *et al.*, 1976b). However, cited experimental studies have shown that experimental dietary- or hyperparathyroidism-induced calcium and phosphate aberrations are not reflected by parallel changes in the fetal blood. Fetal parathyroids function to maintain the calcium homeostasis. Furthermore, hypercalcemia during late gestation is uncommon even in the presence of "physiologic" hyperparathyroidism. Thus, it seems plausible that it is not parathyroid immaturity but postnatal factors that prevent normal PTH reactivity. For example, hypocalcemic hyperphosphatemic premature infants have responded to injections of exogenous PTH with transient rises in serum calcium and magnesium in the first few days of life (Tsang *et al.*, 1973; David and Anast, 1974; Root *et al.*, 1974), indicating that there was bone mineral mobilization in response to PTH (Fig. 4-5, Tsang *et al.*, 1973a), even in infants born prematurely.

In the case of infants with IUGR, such as are commonly born to mothers with toxemias of pregnancy and to young primiparous mothers, significantly lower levels of serum magnesium have been detected than in other low-birth-weight infants (Fig. 4-6, Tsang and Oh, 1970: Jukarainen, 1971). Tsang and Oh (1970) suggested that the low serum magnesium levels in IUGR infants might reflect disturbed placental transfer of magnesium or abnormal fetal magnesium metabolism as part of the intrauterine malnutrition syndrome. Hypocalcemia has been shown to be more striking than hypomagnesemia in IUGR neonates (Tsang *et al.*, 1975). Such neonatal hypocalcemia in infants with placental insufficiency has been associated with impaired

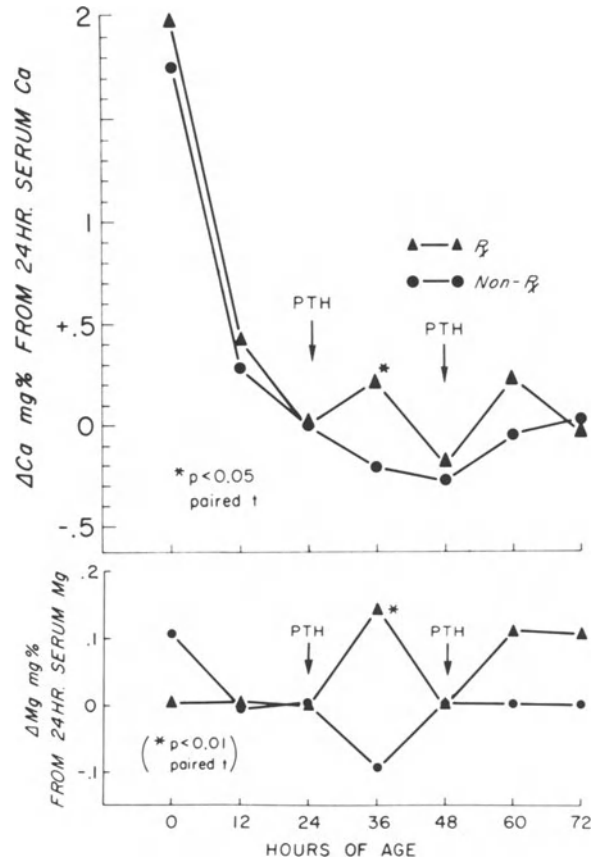

FIGURE 4-5. Mean serum calcium and magnesium in premature infants with and without PTH injections. (From RC Tsang *et al.*: *J Pediat* 83:728–738, 1973.)

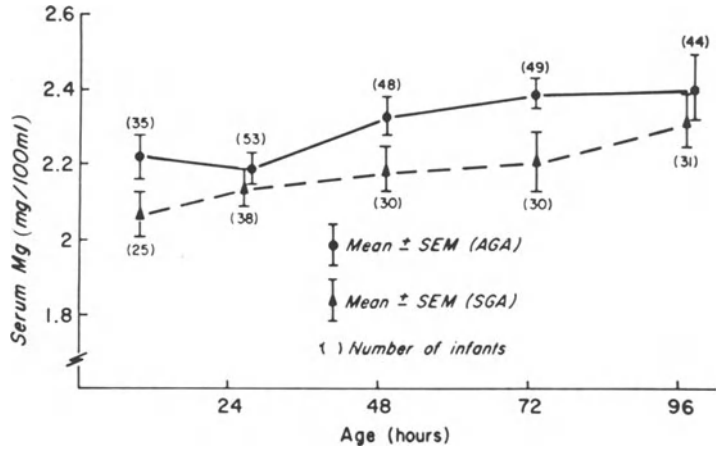

FIGURE 4-6. Serum Mg levels in preterm infants with birth weights appropriate for gestational age (AGA) and small for gestational age (SGA). (From RC Tsang and W Oh: *Am J Dis Child* 120:44–48, 1970.)

transfer of calcium from mother to fetus (Khattab and Forfar, 1971). Tsang *et al.* (1975) suggest that their findings (Tsang *et al.*, 1973a,b, 1974) point toward shortened gestational age or birth asphyxia as more likely explanations of the disturbances in calcium homeostasis during the early neonatal period. The greater tendency of IUGR infants than full-term infants to have poor bone mineralization and spontaneous bone fractures suggests that maintenance of divalent cation homeostasis *in utero* might be achieved by hyperactivity of fetal parathyroids in response to intrauterine malnutrition, when there is faulty placental transport of calcium and magnesium from maternal to fetal circulation.

The observation that IUGR infants often exhibit neonatal hyperirritability and jitteriness (Michaelis *et al.*, 1970; Ferlazzo and Lombardo, 1971; Tsang *et al.*, 1975) suggests that, in addition to hypocalcemia, magnesium deficiency also be considered. The failure to find hypomagnesemia at 4 hours, and its decline by 24–48 hours, especially in infants whose hypocalcemia also becomes more notable at that time (Fig. 4-7, Tsang *et al.*, 1975b), suggests that hypoxia at birth, which is common in

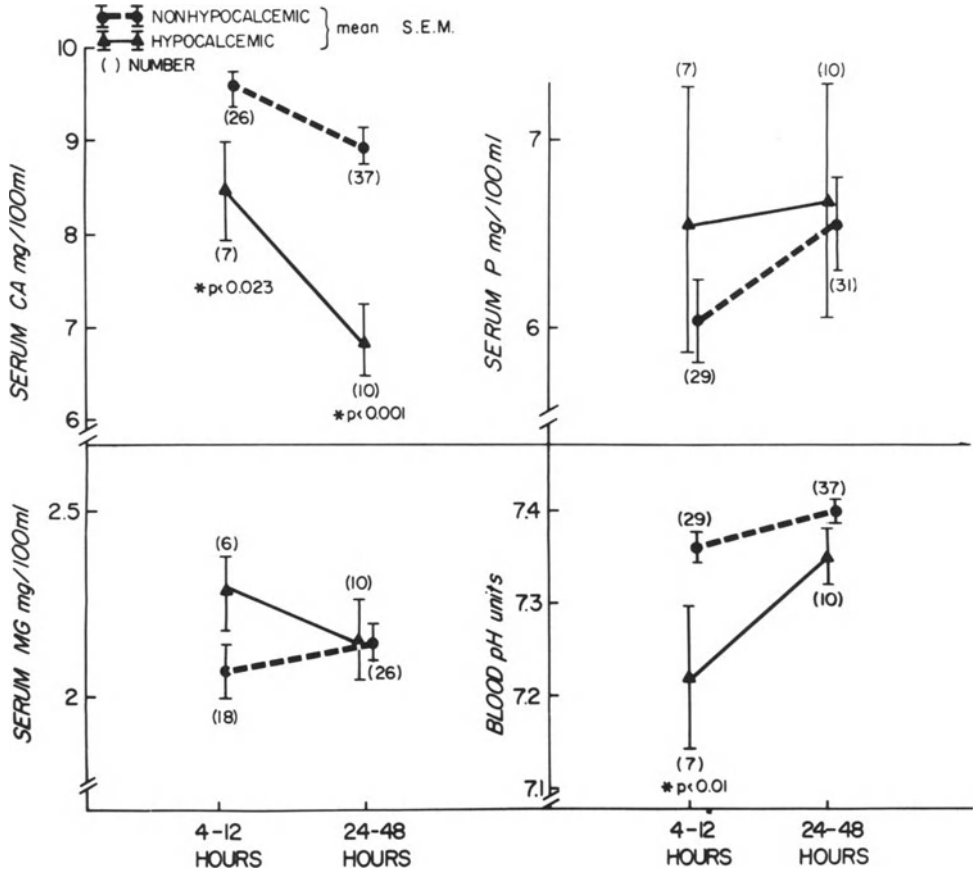

FIGURE 4-7. Serum Ca, Mg, P, and pH in infants with IUGR with and without hypocalcemia. (From RC Tsang *et al.*: *J Pediat* 86:936–941, 1975b.)

IUGR infants (Tsang *et al.*, 1975), can be contributory and might mask the magnesium deficiency. Serum magnesium values being a poor index of tissue magnesium status, percentage retention of magnesium-load tests might prove a more valid means of ascertaining whether the irritability of IUGR infants can be partially attributed to magnesium deficiency (Harris and Wilkinson, 1971; Caddell, 1975).

4.1.3. Neonatal Hypoxia

Infants born after difficult deliveries and who have birth apnea have been found to have hypermagnesemia shortly after birth (Engel and Elin, 1970). It is probable that the source of this elevated serum magnesium is from the tissues, injured as a result of the hypoxia, as has been demonstrated in war injuries and clinical or experimental shock (Beecher *et al.*, 1974; Root *et al.*, 1947; Canepa and Gomez-Pavira, 1965; W. Walker *et al.*, 1968; N . Goldsmith *et al.*, 1969; Flynn *et al.*, 1973, 1976/1980). The accompanying acidosis enhances the shift of bone minerals to the extracellular space (Barzel and Jowsey, 1969; Raisz, 1970). Thus, such infants, despite their transient hypermagnesemia or normal magnesium levels (Fig. 4-8) (Tsang *et al.*, 1974), may actually suffer from body depletion of magnesium. Their drop in serum calcium in the first few days of birth has been generally blamed for the hyperirritability, jitteriness, convulsions, and periods of apnea, common in hypoxic infants (Oppé, 1970). However, they frequently also show as striking depressions in their serum magnesium levels and a lesser drop in serum phosphorus (Fig. 4-9, Tsang *et al.*, 1974). The rise in serum phosphorus, which precedes the rises in the divalent cations, suggests that PTH-mediated mobilization of bone mineral might not then be operative. The rise in serum phosphorus can be caused by several factors. The initially higher than maternal values might be endogenous in that it is caused by endogenous tissue breakdown, which is associated with stress of delivery and birth asphyxia. The subsequent rise might derive from bone mineral efflux, high phosphate intake (from cows' milk), and renal tubular inability to eliminate the phosphorus load in the early days of life. Asphyxiated infants, whose serum magnesium levels dipped only slightly at 12 hours and then rose to normal by 24 hours, were compared with asphyxiated infants whose hypoxemia (starting at 12 hours) persisted through 48–72 hours (Tsang *et al.*, 1974). The hypocalcemia of the latter group was more profound, and correction of acidosis took longer than it did in the asphyxiated infants with normal serum magnesium levels. The drop in serum magnesium levels within 12–24 hours after asphyxia may well reflect the low reserves of magnesium in neonatal infants, or the shift from extracellular to intracellular space on correction of the hypoxia and acidosis.

4.1.4. Neonatal Infants of Diabetic Mothers

Infants of diabetic mothers can either be premature or large for gestational age, often exhibit respiratory distress and acidosis, and also frequently show rising serum phosphorus and falling serum calcium and magnesium levels by 24–48 hours after birth (Fig. 4-10, Tsang *et al.*, 1972). This had been speculated to reflect maternal hyperparathyroidism of diabetic mothers. However, Tsang *et al.* (1972) noted

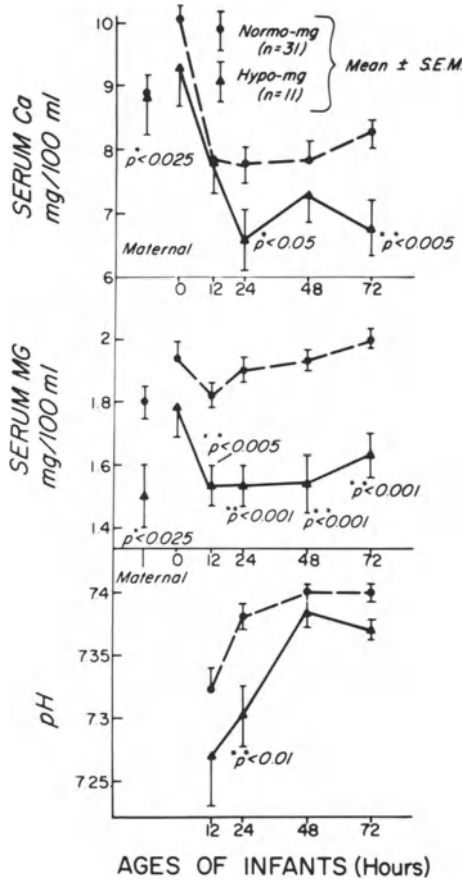

FIGURE 4-8. Serum Ca, Mg, and pH during the first 72 hours of life in infants with birth asphyxia (From RC Tsang *et al.: J Pediat* 84:428–433, 1974.)

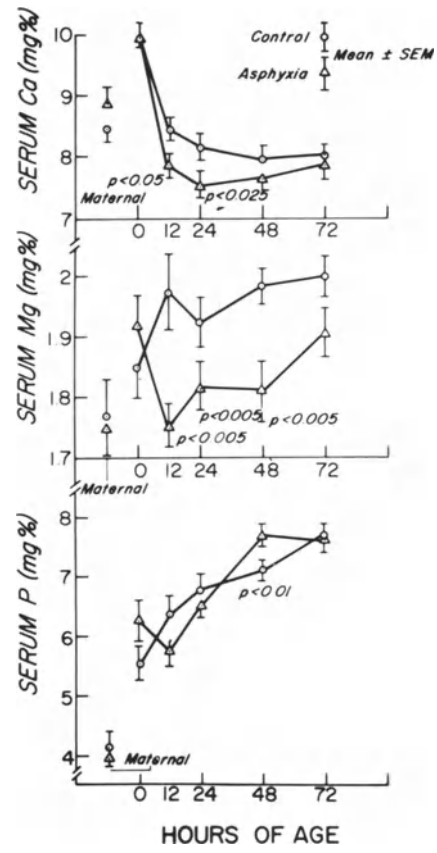

FIGURE 4-9. Serum Ca, Mg, and P at birth, 12, 24, 48, and 72 hours in infants with and without birth asphyxia. (From RC Tsang *et al.: J Pediat* 84:428–433, 1974.)

that diabetic mothers had serum calcium levels within normal limits. Since they did not have hypercalcemia, suppression of fetal parathyroids from this source seems questionable. Functional hypoparathyroidism of the infants was considered unlikely when they were found to exhibit short-term calcemic response to PTH injections (Fig. 4-11), indicating bone mineral mobilization. Although administration of PTH to infants of diabetic mothers caused more phosphaturia than was seen in nontreated infants of diabetic mothers, there was no difference in percentage tubular reabsorption of phosphorus in the two groups, suggesting renal immaturity. Their subsequent work showed no significant difference in serum PTH or total or ionized calcium levels in diabetic than in normal mothers (Tsang *et al.*, 1975). Since they found that PTH levels of cord blood of infants of diabetic mothers (IDM) were not significantly lower than were those of controls, they assumed that the parathy-

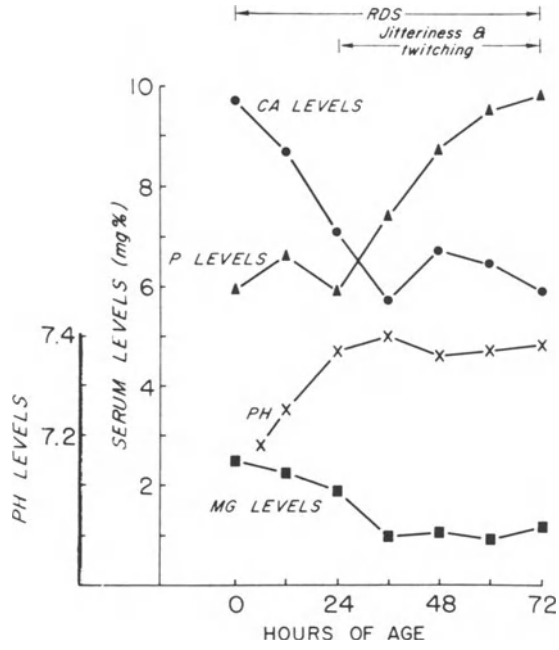

FIGURE 4-10. Serum Mg, Ca, P, and pH in hypomagnesemic, hypocalcemic infants of diabetic mothers. (From RC Tsang *et al.: J Pediat* 80:384–395, 1972.)

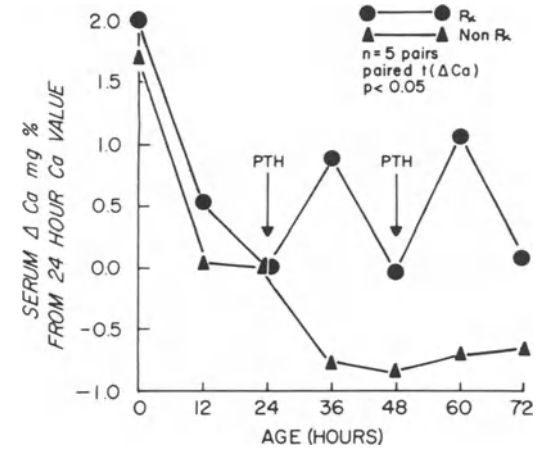

FIGURE 4-11. Calcemic response to PTH of infants of diabetic mothers. (From RC Tsang *et al.: J Pediat* 80:384–395, 1972.)

roids of the IDM functioned as did those of normal infants. The observation that there was no significant increase in PTH levels in response to significant decreases in total and ionized calcium led Tsang *et al.* to assume a failure of production of PTH. Prematurity (9 of 13 infants of insulin-dependent mothers with gestational ages of 37 weeks or less), birth asphyxia (10 of the 28 IDM had 1 minute Apgar scores of 6 or less), and increased calcitonin secretion were also considered as possible explanations for the sustained hypocalcemia of the infants of diabetic mothers. The changes in IDM serum magnesium were not considered significantly different from those of controls in that study. However, although the maternal serum magnesium levels were within the same range in control and diabetic mothers, it is of interest that the cord blood levels of the normal infants, which were low, rose to about 1.7 mEq/liter by 76–96 hours, whereas the mean values of infants of insulin-dependent mothers remained about 1.5 mEq/liter. Their range of values at 24–48 hours was 1.35–1.7 mEq/liter and at 72–96 hours was about 1.4–1.5 mEq/liter. The following year, Tsang *et al.* (1976b) reported that 21 of 56 IDM had serum magnesium levels at or below 1.25 mEq/liter on at least one occasion during the first three days, and that they did not exhibit the normal increase with postnatal age seen in normal infants. Subnormal neonatal serum magnesium levels were related to the degree of severity of diabetes, youth of the mothers, lower gravidity, and prematurity. Lower concentrations of serum magnesium were associated with less increase (or actual decreases) in serum concentrations of PTH from 48–72 hours, and conversely serum concentrations of magnesium at 72 hours were related to parathyroid function from birth to 24 to 48 hours of age (Fig. 4-12, Tsang *et al.*, 1976c). Since diabetes mellitus is recognized to cause magnesium deficiency without the added requirements caused by pregnancy, it is not surprising that infants of diabetic mothers are particularly subject to magnesium deficiency. The interrelationship of their magnesium inadequacy, phosphate excess, and hypocalcemia with their parathyroid malfunction is an important clue to the complex hormonal/mineral interrelationships that may be mediated by a fundamental magnesium deficit.

4.1.5. Neonatal Hypermagnesemia

Hypoxia has been shown to cause loss of magnesium from tissues with resultant elevation of serum magnesium levels. Studies of serum from venously occluded arms (Whang and Wagner, 1966; S. P. Nielsen, 1969) have shown that even short periods of hypoxia cause egress of magnesium from the cells to the blood. Thus, it is not surprising that infants born after difficult deliveries and with birth asphyxia have had elevated serum magnesium levels at birth and shortly thereafter (Engel and Elin, 1970; Donovan *et al.*, 1977b). Such infants, however, often exhibit hypomagnesemia within 12 hours after birth (Tsang *et al.*, 1974), possibly reflecting inadequacy of tissue stores or the shift of extracellular magnesium to the intracellular phase with normal oxygenation.

Acidosis, common in low-birth-weight infants, is another cause of neonatal hypermagnesemia. Even minor drops of muscle pH (to 6.8) has been shown *in vitro* to cause significantly decreased muscle magnesium content (Gilbert, 1961). A clin-

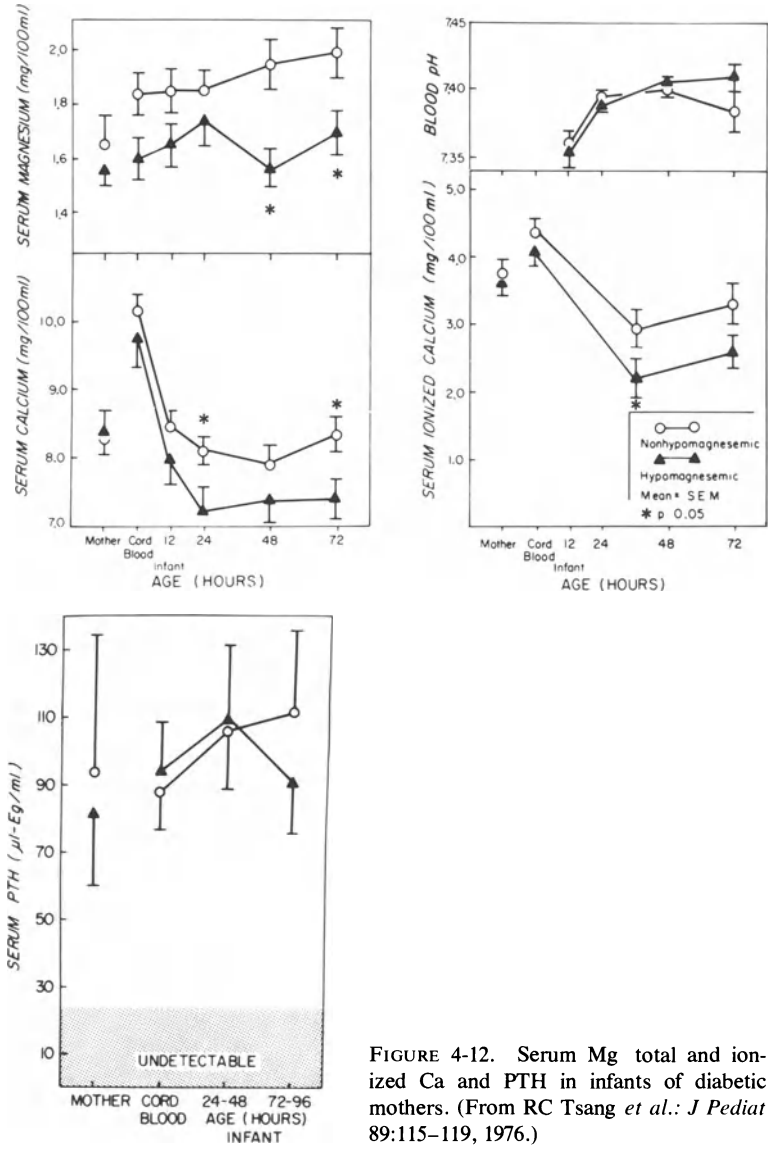

FIGURE 4-12. Serum Mg total and ionized Ca and PTH in infants of diabetic mothers. (From RC Tsang *et al.: J Pediat* 89:115–119, 1976.)

ical reflection of this observation is the hypermagnesemia of decompensated diabetic acidosis (Martin *et al.*, 1958). Thus, the normal or elevated serum magnesium seen in acidotic infants immediately after birth, despite the evidence that such infants are at risk of hypomagnesemia, should come as no surprise. Even normal infants have acidosis, due to elevated maternal lactic acid levels and to the period of anoxia during birth (Acharya and Payne, 1965). The levels fall as oxygenation is established, normally reaching adult values after two days. Infants with respiratory distress have prolonged acidosis and anoxia, which militate against restoring tissue

levels of magnesium. This set of circumstances is likely to mask the underlying magnesium deficiency when serum magnesium levels are relied upon to reflect the magnesium status.

The most intensive study found on the magnesium levels of the neonate (Jukarainen, 1974) demonstrates that high-risk infants with hypocalcemia (whom one would expect to have hypomagnesemia) are likely to have normal magnesium levels in the early hours to days after birth. This investigator correlated many factors that influence neonatal homeostasis, considering gestational and perinatal abnormalities. As many as nine blood samples were analyzed for Mg/Ca/P in the infants during the first five days of life. He found that these longitudinal studies showed that there was an inverse correlation between the serum magnesium and gestational age. The premature and low-birth-weight infants (who have been shown to be more susceptible to hypocalcemic tetany and convulsions) had essentially normal serum magnesium with their hypocalcemia in the first five days, as compared with full-term infants whose hypocalcemia correlated positively with hypomagnesemia during the same period. Infants of diabetic mothers also showed relatively higher serum magnesium levels, in assocation with their hypocalcemia during the first few days, but the magnesium levels tended to drop toward the end of the observation period. Jukarainen (1974) concluded that the inverse relationships between calcium and magnesium levels in the early days of life of the high-risk infants probably reflected disturbed magnesium homeostasis (such as has been seen with hypoxic and acidotic egress of magnesium from the cells).

Direct evidence that this might explain the above findings was provided by Yamashita and Metcoff (1960), who found that the skeletal muscles of premature infants were edematous, and that the levels of normal intracellular cations and of magnesium-dependent enzymes were significantly lower than normal. Chiswick (1971) also noted edema in hypocalcemic neonatal infants, and noted that the serum magnesium levels of the hypocalcemic infants were higher in infants with edema than in those without.

Infants born to mothers given pharmacologic doses of magnesium for eclampsia shortly before delivery have been born with hypermagnesemia and secondary respiratory depression, areflexia, and paralysis (Fishman, 1965; Brady and Williams, 1967; Lipsitz and English, 1967; Lipsitz, 1971). Serum levels as high as 15 mEq/liter were detected in one such infant, who recovered following treatment by exchange transfusion (Brady and Williams, 1967). However, Lipsitz (1971) found no correlation between (1) the cord or newborn serum magnesium levels and the Apgar score; (2) the total dose of magnesium given to the mother and her serum magnesium level at delivery, or that of the cord blood; and (3) the total dose of magnesium and clinical evidence of neonatal magnesium toxicity.

Unlike adults, who excrete infused magnesium rapidly (Chesley and Tepper, 1958), neonates have a very low magnesium excretion rate (Lipsitz, 1971; Tsang, 1972). During the first few days of life, glomerular filtration rates are low (less than 0.34 mg/kg/24 hours); in premature infants the glomerular filtration rate and magnesium excretion is even less than in full-term infants (Tsang, 1972). Thus, it is not surprising that it has taken up to five days for neonatal hypermagnesemia to fall to normal levels (Lipsitz, 1971). Despite sustained elevated serum magnesium levels

in infants born to toxemic mothers, given large amounts of magnesium for different periods of time before delivery, there have been surprisingly few instances of serious manifestations of hypermagnesemia. For example, only 8 of the 118 infants born to mothers given 30–40 g of magnesium sulfate i.m. during the 24 hours before delivery, had Apgar scores of 5 or less; none had cord magnesium levels above 6 mEq/liter during labor; no detectable adverse effects attributable to the magnesium alone were detected (Hutchinson *et al.*, 1963).

The meconium plug syndrome, attributed to hypermagnesemic suppression of peristalsis, has been reported in two infants born prematurely to two eclamptic young women given high-dosage magnesium therapy shortly before delivery (Sokal *et al.*, 1972). The cord blood serum magnesium level was 8.3 mEq/liter in the infant from whom it had been obtained; it was 6.0 mEq/liter at 3 hours of age in the other. It had dropped to 5.4 mEq/liter by 6 hours, 4.3 at 55 hours, to 4.3 mEq/liter in the first infant, and to 4.2 mEq/liter at 10 hours in the second. Neither had hypocalcemia at any time tested. Since epsom salt enemas have been known since the turn of the century to cause magnesium toxicity in children and adults (C. Fraser, 1909; Fawcett and Gens, 1943), this treatment of hyaline membrane disease, which has led to fatal consequences of severe hypermagnesemia, is no longer recommended (Tsang, 1972; Outerbridge *et al.*, 1973).

4.1.6. Magnesium Depletion by Exchange Transfusions with Citrated Blood

Exchange transfusions with blood to which acid-citrate-dextrose (ACD) solution has been added are known to cause infantile hypomagnesemia (Dooling and Stern, 1967; Bajpai *et al.*, 1967a,b; Z. Friedman *et al.*, 1971,1972). Although it has long been known that weakly dissociated salts of citrate are formed with both magnesium and calcium (Hastings *et al.*, 1934; Walser, 1961), and citrate infusions to dogs have caused both hypomagnesemia and hypocalcemia [total (Bunker *et al.*, 1962) and ionized (Killen *et al.*, 1971)], the customary procedure for infants receiving exchange transfusions who develop irritability, seizures, or cardiac arrhythmias (Dooling and Stern, 1967; Rosefsky, 1972) has been to provide calcium with the transfusion and to monitor the serum calcium levels. Generally, only when the condition fails to improve has the magnesium status been explored and magnesium therapy instituted. An editorial (*Canad MAJ*, 97:868, 1967) considered sudden death during the course of the exchange a possible consequence of the citrate-induced reduction in serum ionic magnesium. Two groups of investigators in Canada demonstrated that the serum ionic magnesium dropped substantially during exchange transfusion with ACD blood (Bajpai *et al.*, 1967a,b; Z. Freidman *et al.*, 1971, 1972). The first group (Bajpai *et al.*, 1967b) noted electrocardiographic changes (flattening of T waves) when the serum Mg^{2+} fell below 0.8 mEq/liter. The second group (Z. Friedman *et al.*, 1972) considered it likely that the magnesium-responsive arrhythmia that developed during the fourth ACD plus calcium transfusion (Rosefsky, 1972) was likely to have reflected also a reduction in ionic calcium, despite the administration of calcium gluconate. A more detailed report (Radde *et*

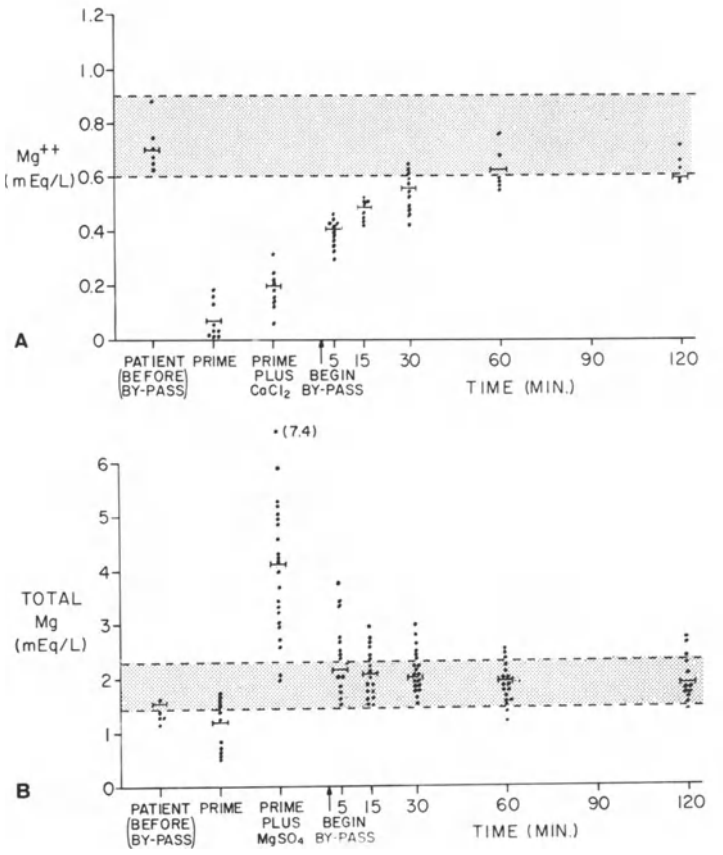

FIGURE 4-13. Ionized plasma magnesium in cardiopulmonary bypass patients with ACD prime without (A) and with (B) added magnesium. (From DA Killen *et al.*: *Ann Thorac Surg* 13:371–379, 1972.)

al., 1972), presented evidence that abnormal symptoms and signs are found almost exclusively in infants whose plasma levels of both cations were below the lower limits of normal. Recently Donovan *et al.* (1977a) showed that exchange transfusion (which they confirmed lowered serum levels of ionized magnesium and calcium) increases PTH levels, as measured by immunoassay.

An overload of citrate similar to that of the exchange transfusion of infants is the use of ACD blood prime in cardiopulmonary bypass procedures. Killen *et al.* (1972) showed that severe depression of ionized magnesium (Fig. 4-13A) could be prevented by adding magnesium sulfate: 3 ml of 10% solution per unit of ACD blood (Fig. 4-13B). Since low magnesium levels are common in patients to undergo open-heart surgery, magnesium therapy of such patients is often necessary (Holden *et al.*, 1972; Khan *et al.*, 1973).

When transfusions, using citrated blood, are given to those whose underlying condition makes it likely that they might be magnesium deficient before the trans-

fusion, severe depletion may ensue. Jalbert *et al.* (1969) reported such an instance in the case of a premature infant born to a preeclamptic mother. The infant developed mucoviscidosis and intestinal obstruction requiring resection, during which citrated blood transfusions were given. Calcium-refractory seizures developed that responded only to magnesium repletion.

4.1.7. Low Ionized Calcium and Hypomagnesemia

In view of the drop in ionized calcium and magnesium caused by citrated blood transfusions, attention should be paid to other more common conditions in which neonatal tetany has been correlated with decreased ionized calcium levels. (Ionized magnesium is less readily measured, and thus is rarely reported.) The possibility that asymptomatic neonatal hypocalcemia might be related to normal levels of ionized calcium despite low total calcium has long been suspected (Bruck and Weintraub, 1955) and more recently verified. Bergman (1972) showed that symptomatic neonatal hypocalcemia is associated with lower levels of ultrafiltrable fractions of calcium than of total calcium. On the other hand, D. M. Brown *et al.* (1972) measured the ionized fraction of calcium, and found no correlation between low ionized calcium levels and symptomatic hypocalcemia. Sorell and Rosen (1975) found symptoms with decreases in ionized calcium to a critical level of 2.5 mg/100 ml. Bergman (1974) showed that up to 10–12 hours after birth, the decrease in total calcium is mostly caused by a decrease in the ultrafiltrable fractions. Since symptomatic hypocalcemia seems to be better related to lesser decreases in ultrafiltrable calcium that consists of ionized calcium plus complexed calcium (about 14% of total calcium: Walser, 1961) than to the ionized fractions, it may be speculated that the change from asymptomatic to overt hypocalcemia might be contributed to by a drop in the complexed fraction. It can be presumed that the HPO_4 fraction is unlikely to be low in a condition associated with hyperphosphatemia. The citrate fraction, which is dependent on vitamin D, seems a likely candidate for consideration. It is a complex question, however, since vitamin D deficiency (in rats) has been correlated with decreased blood and bone citrate levels (Harrison *et al.*, 1957). Vitamin D administration to rachitic rats has raised the citrate levels (Steenbock and Bellin, 1953), but excess vitamin D (as in acute infantile hypercalcemia related to hyperreactivity to vitamin D) is associated with subnormal blood citrate levels (Forfar *et al.*, 1959; Lindquist, 1962). Radde *et al.* (1972) found that, at least in newborn infants, symptomatic hypocalcemia only occurred when low ionized calcium levels were present with concomitant hypomagnesemia, an interesting observation in view of the vitamin D resistance of magnesium-deficient patients. Sorell and Rosen (1975), finding both normal and low serum magnesium levels in symptomatic hypocalcemia, did not confirm the report of Radde *et al.* (1972). However, of the seven infants and young children they reported, all but one (who had sepsis and thus might have had acidosis) had hypomagnesemia. The other two with normal serum magnesium levels in their series of nine were 17- and 19-year-old patients with renal failure, a condition that has been associated with tissue magnesium depletion despite even hypomagnesemia (Lim and Jacob, 1972c). One of the infants developed hypomagnesemia and hypocalcemia after cardiac surgery.

4.2. *Treatment of Infantile Conditions Associated with Abnormalities of Magnesium*

4.2.1. *Correction of Neonatal Acidosis*

When acidosis develops in the newborn infant, it is customary to treat it with sodium bicarbonate or sodium lactate. Unfortunately, the conditions that give rise to acidosis not infrequently are associated with magnesium egress from the cells. Infusions of sodium lactate cause substantially increased urinary output of magnesium (Barker *et al.*, 1959). Thus, the production of negative magnesium balance in infants whose postoperative acidosis was thus corrected, and the production of hypomagnesemia (Atwell, 1966), is not surprising. (The stress of surgery also increases magnesium loss.) Correction of renal acidosis with lactate, citrate, or bicarbonate has also caused hypomagnesemia (Randall, 1969). Administration of sodium bicarbonate to acidotic neonatal infants has reduced serum ionic calcium levels (Radde *et al.*, 1972; Tsang *et al.*, 1977a,b) and has also lowered serum magnesium levels (Radde *et al.*, 1972; Jukarainen, 1974). The higher the serum bicarbonate levels, the lower the serum magnesium levels (Jukarainen, 1974).

4.2.2. *Intensification of Magnesium Deficiency by Treatment of Hypocalcemia with Calcemic Agents*

It has been reiterated that infants with hypomagnesemia should not be treated with calcium or vitamin D (Tsang *et al.*, 1977a; Seelig, 1978/1980). Nonetheless, since hypocalcemia is usually detected first in convulsing infants (magnesium determinations often being obtained only on failure of calcemic therapy to correct either the symptomatic or biochemical abnormalities), calcium alone or with vitamin D is still usually the first approach. In fact, prophylactic administration of calcium has been recommended for low-birth-weight or asphyxiated infants who are at particular risk of hypocalcemia (D. R. Brown *et al.*, 1976; Salle *et al.*, 1977). It is realized and cautioned that when symptomatic infantile hypocalcemia is found, hypomagnesemia should be sought (Editorial, *Brit. Med. J.*, 1973; Tsang *et al.*, 1977a). The observation that symptomatic infantile hypocalcemia develops almost exclusively when there is concomitant hypomagnesemia (Radde *et al.*, 1972) lends support to the importance of seeking out a magnesium deficit. Since magnesium is predominantly an intracellular cation, and since levels in the blood are generally kept within narrow limits, relying on serum magnesium as the index of magnesium status of the body can give misleading information. This is particularly true for neonatal infants, whose serum magnesium can be elevated as a result of acidosis or asphyxia-induced egress of magnesium from tissue. The parenteral magnesium-load test is more reliable as a clue to magnesium depletion. For example, Harris and Wilkinson (1971) found that of nine infants suspected of magnesium deficiency, who had serum magnesium levels that were normal, four were deficient by the loading test, Byrne and Caddell (1975) found that there were infants in their survey whose magnesium deficiency would not have been detected by serum levels alone.

With high-risk infants, whose body stores of magnesium might be precariously

low, it is possible that treatment directed toward correction only of hypocalcemia might thereby not only fail to correct convulsions, but might intensify occult cardiovascular and renal lesions. Such damage is caused by experimental magnesium deficiency, and is worsened by calcium, phosphate, and vitamin D excesses. Among infants with severe imbalances (low Mg/high Ca, P, vitamin D intakes), the damage might be severe enough to cause acute and chronic signs and symptoms during infancy, leading to early death or chronic disorders that might be termed "congenital." Among those with less marked imbalances (i.e., whose prenatal stores were higher or whose postnatal calcemic challenges were less, there might be lesser degrees of damage that might lay the groundwork for adult cardiovascular and renal disease.

It seems likely, even though magnesium determinations had not been made, that the two infants described by D. Andersen and Schlesinger (1942) might have reflected the first of the two possibilities: convulsive hypomagnesemic hypocalcemia treated with calcemic agents, resulting in death in the fourth month of life. In addition to administration of calcium gluconate and moderately to extremely high doses of vitamin D (that lowered, rather than raised, the serum calcium levels) both infants were also given repeated blood transfusions for refractory anemia, and both were treated repeatedly for refractory acidosis. It is conceivable that the anemia was a sign of magnesium deficiency (Elin, 1973, 1976/1980). It is plausible that the calcium- and vitamin-D-refractory hypocalcemic neuromuscular irritability and seizures of both infants might have been caused by early magnesium deficiency that interfered with response to the calcemic agents, and that was intensified by that treatment and by the use of citrated blood for the anemia, and lactate and bicarbonate for the acidosis. One vomited several times daily and developed hypercholesterolemia; the other developed hypertension—all signs of vitamin D excess and in the case of increased blood pressure of a high Ca/Mg ratio. Both had peripheral and coronary arteriosclerosis; one had myocardial infarctions and the other had cardiomegaly. Both had severe renal damage: one predominantly fibrous replacement; the other (who had been given 300,000 IU vitamin D) also had renal calcinosis. Although their biochemical findings suggested hypoparathyroidism, they both had hypertrophied parathyroid glands and bone pathology, and were diagnosed at autopsy as having renal hyperparathyroidism. In view of the data reviewed in the foregoing section, the possibility that these infants had hyperparathyroidism secondary to magnesium deficiency, and that the deficiency interfered with the response of target organs to PTH (pseudohypoparathyroidism) or to vitamin D, and led to cardiovascular and renal disease should be seriously considered. Almost a quarter of a century later, severe hypomagnesemia (0.8 mEq/liter) was correlated with high-dosage vitamin D and calcium treatment of an infant whose hypocalcemic convulsions had started at one month (Salet *et al.*, 1966), as in the prior two cases. Treatment with both cations was then instituted, with resultant elevation of low calcium levels to normal. Both hypocalcemia and hypomagnesemia (0.3 mEq/liter) recurred at three months, after treatment had been stopped. The baby again responded to combined cation therapy. When treatment was again stopped, he exhibited hyperphosphatemia, as well as hypocalcemia. PTH administration corrected the blood calcium and phosphorus levels, but lowered the blood magnesium

level (0.5 mEq/liter). Vitamin D therapy again intensified the biochemical abnormalities and the convulsions. Like the infants described by Andersen and Schlesinger (1942) this infant's findings suggested hypoparathyroidism. However, his hypomagnesemia was identified early and treated intermittently until it became manifest that his vitamin-D-resistant hypocalcemia was secondary to magnesium malabsorption. This group found that high-dosage vitamin D increased his magnesium requirements and that treating with both magnesium and calcium was not as effective in raising cellular magnesium to normal levels as was treating with magnesium alone. They later found that this infant's magnesium malabsorption was familial, when a sibling was born with the same defect (Salet *et al.*, 1970). High dosage vitamin D (100,000 IU daily) for familial hypoparathyroidism and convulsive hypocalcemia resulted in hypomagnesemia in a baby from a family with a high incidence of convulsions (Niklasson, 1970). This infant developed emotional lability and mental retardation, similar to that seen with hypervitaminosis D (Review: Seelig, 1969b). Her young sister later also developed hypomagnesemia. It was noted that infantile convulsions, with death during infancy (including one sudden unexplained death at four weeks), were common in the family of these sisters, whose parents were first cousins. The possibility that there was primary magnesium malabsorption or renal magnesium wasting in this family was not explored. The infant son (ninth child of a mentally retarded mother), who developed convulsions after three months of vitamin-D-supplemented (400 IU/day) dried milk formula, was the fifth son to develop seizures (Vainsel *et al.*, 1970). Intravenous calcium gluconate and high dosage vitamin D (750,000 units per week) raised the serum calcium to low normal levels, but failed to control the seizures. Hypomagnesemia (0.4–0.7 mEq/liter) was then identified, and magnesium therapy was begun three days before death. He had microfocal myocardial necrosis, intraluminal calcium deposits in the renal tubules, and glomerular fibrosis. He, like the brother who had had post mortem examination, had cerebral arteriosclerosis. Whether the mentally retarded mother had the genetic defect that led to convulsions and cardiovascular lesions in her sons, who might have been susceptible to earlier (fatal) manifestations of magnesium deficiency, having been born in rapid succession and thus probably with low stores of magnesium, is speculative. The infant who developed neonatal fits at eight days of life that did not respond to pyridoxine, glucose, or calcium therapy, but immediately improved following magnesium administration, had been born to a mother with celiac disease (Davis *et al.*, 1965), and thus probably had low body stores of magnesium.

It is provocative that calcium, vitamin D, and sometimes PTH were used to control the neuromuscular irritability and to correct the hypocalcemia of almost all the infants and children ultimately found to be suffering from magnesium malabsorption. Their serum calcium generally rose, sometimes to hypercalcemic levels, but their clinical signs persisted (with lowered serum magnesium levels) until their magnesium deficiency was diagnosed and corrected. Infants with severe gastroenteritis or with PCM have also developed hypomagnesemia during the recovery period, while being fed diets rich in calcium, vitamin D, and protein.

Similarly, calcium therapy has not been effective in controlling postoperative seizures, or those developing after exchange transfusion, whereas magnesium ther-

apy corrected the convulsions and both the hypocalcemia (Atwell, 1966; Dooling and Stern, 1967; Jalbert *et al.*, 1969). Even feeding vitamin-D-fortified cows' milk to an infant recovering from a colostomy was found to produce hypomagnesemic (0.5 mEq/liter) convulsions that responded promptly to magnesium repletion (Savage and McAdam, 1967). Wilkinson and Harris (1969), who tested surgically treated infants for magnesium deficiency by the parenteral magnesium-load test (Thoren, 1963), found that there was severe depletion in 5 of 9 of their patients. In their further study, they found that 20 of 29 infants (many of whom had undergone gastrointestinal surgery) retained sufficient of the loading dose of magnesium to indicate deficiency, despite normal serum magnesium levels in four of nine whose serum levels were also measured.

Thus, the frequently spontaneous reported restoration of serum magnesium levels to normal, following moderate calcium treatment of infantile convulsions (David and Anast, 1974; D. R. Brown *et al.*, 1976; Salle *et al.*, 1977), is not absolute evidence that magnesium deficiency might not still be present. As had been indicated, there have been many instances of profound intensification of overt manifestations of infantile hypomagnesemic hypocalcemia by treatment with calcemic agents. In 1973, Volpe distinguished "jitteriness" from neonatal seizures, and commented that if hypocalcemic convulsions are refractory to calcium gluconate infusions, hypomagnesemia should be sought and treated by adding 2–3% magnesium sulfate (2–6 ml) to the intravenous infusion. He more recently (1977) commented that calcium infusions should not be given routinely to all newborns during their initial seizures, and recommended that if hypomagnesemia is present the magnesium should be given intramuscularly (0.2 ml/kg of 50% $MgSO_4$) rather than intravenously. He noted that about half of newborns with seizures secondary to later-onset hypocalcemia also have hypomagnesemia, and that calcium administration to such infants may aggravate the hypomagnesemia and maintain the convulsive state.

It is not known whether the "jitteriness" of infants (such as is described in infants who died of the SIDS) is equivalent to the tremor syndrome reported from India as a manifestation of infantile magnesium deficiency (Wong and Teh, 1968; Chhaparwal *et al.*, 1971b, 1971/1973). Wong and Teh (1968) observed 13 of a series of 40 babies with convulsions or tremors of infancy who had hypomagnesemia in the absence of hypocalcemia. The remainder were low in both cations. Tremors, that developed on the first to third day of life (associated with serum magnesium levels of 0.66–1.14 mEq/liter) promptly responded to intramuscular 50% $MgSO_4$ (0.5–1.5 ml/24 hours). A feeble infant, who had required resuscitation, and another whose tremors did not develop until the 30th day of life, required many injections to manage the recurrent tremors. These investigators also reported seven additional infants and young children with hypomagnesemic normocalcemic tremors responsive to magnesium therapy. They commented that the 13 babies with hypomagnesemia alone could not be clinically differentiated from 27 additional infants and young children who had hypocalcemia with and without hypomagnesemia. Radde *et al.* (1972), in their study of concomitantly low total magnesium and ionized calcium in infants with symptomatic hypocalcemia, also reported an occasional infant with convulsive hypomagnesemia alone. Cockburn *et al.* (1973) found only hypomagnesemia without hypocalcemia in 7% of their series of 75 convulsing newborn

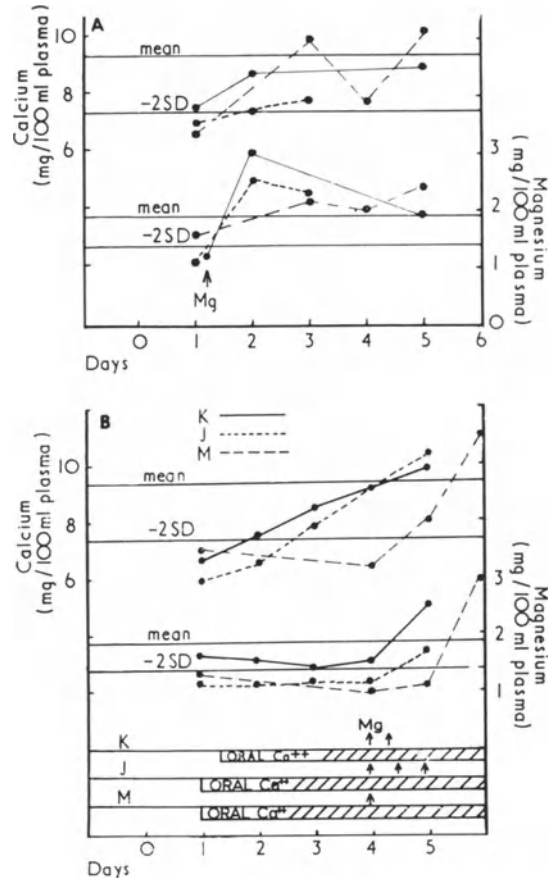

FIGURE 4-14. Response to infantile hypocalcemia to i.m. magnesium. (A) Effect of magnesium on serum calcium concentrations in neonatal hypocalcemia (three cases). (B) Effect of magnesium on serum calcium concentrations in three cases in which oral calcium had failed to relieve hypocalcemia. Arrows indicate i.m. administration of magnesium. Day 1 is the day of the first convulsion. (From F Cockburn *et al.*: *Arch Dis Childh* 48:99–108, 1973; courtesy of JO Forfar, 1978.)

infants. In almost 80% there were combined mineral disturbances, low magnesium and calcium in half. "Jitteriness" was seen in 36% of those with hypomagnesemia and hypocalcemia. Forfar's group (Cockburn *et al.*, 1973) commented that in the beginning of their study, before they realized the importance of hypomagnesemia in maintaining hypocalcemia and convulsions, they routinely gave calcium gluconate oral supplements to such infants. Calcium infusions were added if convulsions persisted. Later, treatment with 0.2 ml/kg 50% $MgSO_4$ became routine. They found that giving intramuscular magnesium was more effective in raising the serum calcium than was oral calcium (Fig. 4-14A). With this treatment it became unnecessary to administer calcium intravenously. In fact, the found that magnesium alone restored both normal magnesium and calcium levels (Fig. 4-14B). They cautioned

against overdosing with magnesium during the neonatal period, because of the risk of neuromuscular blockade, and allowed only two doses of magnesium per infant before redetermining serum levels. Four years later, this group analyzed the comparative results of treating neonatal tetany with magnesium sulfate alone, calcium alone, or a barbiturate (Turner *et al.*, 1977). Among 10,500 live births over a 2½-year period there were 104 infants with symptomatic hypocalcemia that started at 4 to 8 days of age. They were randomly allocated to three treatment groups: 34 were given calcium gluconate (10 ml of 10% solution orally with each feed for 48 hours); 33 were given phenobarbitone (7.5–15 mg at 6-hour intervals); 37 were given 0.2 ml/kg 50% $MgSO_4$ intramuscularly. Mean posttreatment plasma calcium and magnesium levels were significantly higher in the magnesium-treated group than in either of the other groups, and the number of convulsions and number of treatments necessary to control the convulsions significantly lower (Table 4-1). Only one infant in the magnesium-treated group was still convulsing after 48 hours treatment, whereas 13 and 10 were still convulsing after 48 hours of calcium and barbiturate therapy, respectively (significance: $p = 0.001$). This group found the magnesium therapy to be free of major side effects, provided it is injected deep into the muscle, and recommend that magnesium sulfate is the treatment of choice for infantile hypocalcemic convulsions, whether or not hypomagnesemia is present. Paunier *et al.* (1974), who first detected the primary magnesium malabsorption syndrome (Paunier *et al.*, 1965) has commented that the clinical syndrome of hypomagnesemia is indistinguishable from that of hypocalcemia. When the magnesium deficit is severe, as in the genetic disorder, he recommends intramuscular administration of 0.5–1 mEq of magnesium/kg body weight. He, too, cautions against intravenous administration because of the effect of hypermagnesemia on cardiac and neuromuscular conduction. Those with chronic hypomagnesemia are given 1–2 mEq/kg of oral magnesium salts in divided doses.

In view of the risk that not only convulsive disorders, which demand immedi-

TABLE 4-1. Pre- and Posttreatment Plasma Magnesium, Calcium, and Phosphorus in Response to Treatment of Neonatal Tetany[a]: Results of Treatment with Magnesium, Calcium, or Phenobarbitone (Mean ± SD)

	Magnesium therapy ($N = 37$)		Calcium therapy ($N = 34$)		Barbiturate therapy ($N = 33$)	
	Pre-R	Post-R	Pre-R	Post-R	Pre-R	Post-R
Plasma magnesium (mEq/liter)	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/100 ml)	6.16 ± 0.64	8.19 ± 0.97	5.80 ± 0.72	7.24 ± 1.12	6.11 ± 0.66	7.05 ± 1.06
Plasma phosphorus (mg/100 ml)	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	1.86 ± 0.9	(After R started) 3.24 ± 4.23	1.72 ± 0.9	(After R started) 8.36 ± 10.2	1.67 ± 0.8	(After R started) 8.93 ± 9.4
Number of doses required for cure	2.31 ± 0.5		15.63 ± 5.9		12.48 ± 5.8	

[a]Adapted from Turner *et al.* (1977).

ate attention, are a risk of calcemic rather than magnesium therapy, this author supports the conclusion of Forfar's group (Turner *et al.*, 1977) that magnesium, not calcium, is the treatment of choice. Another caution must be given, applicable to infants and children whose hypocalcemia has been under treatment with such a calcemic agent as vitamin D. When magnesium is given to such patients, some respond to previously given vitamin D (which as a fat-soluble vitamin is stored) by developing sudden hypercalcemia. Durlach (1961), who observed that vitamin D therapy (in normocalcemic tetany) is effective only when the magnesium deficit is repaired, later cautioned that magnesium therapy restores the hypercalcemic response to high-dosage vitamin D, and that its administration should be carefully monitored by measurement of serum calcium when treating with magnesium (Durlach, 1969a, 1971). The observation that hypercalcemia has developed when magnesium therapy is added to high-dosage calcium and vitamin D therapy (i.e., of vitamin-D-resistant rickets: Rösler and Rabinowitz, 1973) suggests that release of PTH (Review: Anast, 1977), its conversion to an active form (Passer, 1976), or response to vitamin D might be subnormal in the presence of hypomagnesemia.

On the other hand, the classic treatment of vitamin-D-resistant osteopenias, which are usually associated with hypocalcemia, is with pharmacologic doses of calcemic agents. Vitamin D and its new metabolites are the most frequently used agents. It is well to recall that vitamin D poisoning is a risk, whether in the treatment of hypoparathyroidism (Leeson and Fourman, 1966a,b) or in the treatment of vitamin-D-refractory rickets (Paunier *et al.*, 1968a; Moncrieff and Chance, 1969). It is proposed that evaluation of the magnesium status, and a trial of magnesium therapy be given in vitamin-D-refractory rickets. It is conceivable that the magnesium might suppress the secondary hyperparathyroidism, thereby correcting the phosphaturia, and it might enhance both bone mineralization and formation of normal matrix.

4.3. Influence of Infant Feeding on Magnesium Status: Interrelations with Calcium, Phosphorus, and Vitamin D

The first reference found, with data on plasma magnesium as well as calcium levels in infants and young children, included 38 patients with magnesium determinations, 24 of which were low (Denis and Talbot, 1921). Half of those with hypomagnesemia (< 1.40 mEq/liter) were listed as having feeding problems (cited as "regulation of feeding"). Ten of those 12 had concomitant hypocalcemia (1.0–6.8 mg/100 ml) and 1 had hypercalcemia (12.9 mg/100 ml). Most studies since then have stressed hypocalcemia as the predominant factor in neonatal tetany, a syndrome seen almost exclusively in bottle-fed infants. The higher phosphorus/calcium ratio of cows' milk, as compared to human milk, has been usually blamed. However, as the importance of hypomagnesemia has been recognized in many infants with hypocalcemic tetany, the high phosphorus/magnesium ratio of cows' milk has also been considered. The possibility of transient hypoparathyroidism and renal tubular immaturity has each been investigated as the explanation of the neonate's failure to correct the often long-sustained hyperphosphatemia that is derived principally from

cows' milk. Forgotten is a provocative preliminary report (Swanson, 1932) that showed that an infant fed cows' milk from one to three months of age retained much more calcium than he did phosphorus or magnesium as compared with an infant of the same age fed human milk. When vitamin D_3 (in cod liver oil) was added to the regimen of both infants at three months of age, their daily retention of all three elements rose. The differences in mineral retentions effected by the addition of vitamin D is mentioned here because the formulas administered in most of the subsequent comparative studies incorporated vitamin D; most infants receiving human milk were not so supplemented. Thus, the contrasting findings in breast-fed and formula-fed infants can be a consequence, not only of the higher mineral content and different phosphorus/mineral ratios, but a consequence of the difference in vitamin D supplementation. Not resolved is what happens to the excessive minerals retained by cows'-milk-fed infants. Manifestly, as indicated by the hypocalcemia and hypomagnesemia of artificially fed infants, the retained divalent cations must reach tissue sites, from which, probably as a result of horomonal imbalances, they are not readily mobilized.

4.3.1. Human versus Cows' Milk

The mineral content of human milk is considerably less than that of cows' milk (Table 4-2), the cows' milk being suited to the needs of the calf, which grows much more rapidly than does a human infant. The ratios of phosphorus to magnesium and calcium in the reconstituted dried cows' milk used in Scotland, and human milk, have been given by Cockburn *et al.* (1973) as follows:

	Cows' milk	Human milk
P/Mg	7.5/1	1.9/1
P/Ca	0.8/1	0.2/1

The excessive phosphorus in cows' milk contributes to the abnormalities of serum levels of both calcium and magnesium, not only because of the higher dietary intake of phosphorus in formula-fed babies but because of functional factors (parathyroid and renal) that interfere with adequate elimination of the phosphate load and interfere with mobilization of bone minerals. The earlier studies stressed the

TABLE 4-2. Minerals in Human and Cows' Milk[a]

Mineral	Human milk (mg per 100 g)	Cows' milk (mg per 100 g)
Magnesium	4.0	13.0
Calcium	33.0	118.0
Phosphorus	14.0	93.0
Potassium	51.0	114.0
Sodium	16.0	50.0

[a] From composition of foods, Agriculture Handbook No. 8 U.S. Department of Agriculture, 1963.

TABLE 4-3. Retention of Minerals in Full-Term Infants On Human and Cows' Milk Without and with Vitamin D_3[a]

	Magnesium		Calcium		Phosphorus	
	Daily[c]	Total[d]	Daily[c]	Total[d]	Daily[c]	Total[d]
Infant on human milk (pooled)						
1–3 months	0.20	8.97	0.10	4.7	0.81	37.2
3–6 months (with cod liver oil)[b]	0.37	15.50	1.79	74.4	1.48	61.6
Infant on whole cows' milk						
1–3 months	0.82	32.90	2.87	117.0	2.97	119.0
3–6 months (with cod liver oil)	0.63	23.90	7.28	279.0	4.47	171.0

[a] Data from Swanson (1932).
[b] Cod liver oil: 1 tsp. twice daily.
[c] Daily retention: mM/day.
[d] Total retention: mM/kg gain in weight.

phosphorus and calcium. The importance of magnesium in calcium homeostasis has been increasingly recognized, and more attention is now being paid to magnesium levels and to the influence of hypomagnesemia on hormonal function and calcium homeostasis.

Still largely disregarded is the role of the intake of vitamin D, despite the occasional comparative study of serum calcium, magnesium, and phosphorus levels in breast-fed versus bottle-fed infants that suggest the need for further work in this area.

4.3.1.1. Metabolic Balances of Infants Fed Human or Cows' Milk

The early long-term metabolic study (Swanson, 1932) performed on two infants 10–14 days to 6 months of age: one fed on pooled human milk except for a 1-week cows'-milk-consumption comparative period, and one fed cows' milk throughout, contains much thought-provoking data. This is the only study found in which the effect on mineral retention of whole cows' milk (without added vitamin D) was recorded. It also provides data on the change in mineral retention caused by addition of vitamin D_3 (1 teaspoon cod liver oil) to the regimens of both infants, starting at three months of age (Table 4-3), although there were no signs of rickets. The ratios of mineral retention for the infant fed human milk to those for the cows'-milk-fed infant were:

	Human-milk-fed/cows'-milk-fed	
	Months 1–3	Months 3–6 (with cod liver oil)
Mg	1/3.6	1/1.2
Ca	1/25.0	1/3.8
P	1/3.1	1/3.1

The infant given human milk was switched to cows' milk for a 5-day metabolic period, before being continued on his usual regimen. During that period, his cumulative phosphorus retention increased twofold over each of the previous two 6-day metabolic periods; his cumulative calcium and magnesium retentions rose about fourfold over the average of the previous two periods. Shifting back to breast milk resulted in reversal of magnesium and calcium retentions to near prior values, but in a sharp (over tenfold) drop in phosphorus retention. Administration of cod liver oil to the infant on human milk initially resulted in a fall in retention of calcium, but there was a rapid increase thereafter, with an average daily retention in the last two metabolic periods more than tenfold greater than before the supplement was given. The average increases in daily phosphorus and magnesium retention were moderate, although phosphorus retentions rose much more in the last weeks of the study than in the first weeks after the vitamin D had been added (2–5 mM/6-day period to 12–15 mM/6-day period). Administration of cod liver oil to the infant on cows' milk increased his retention of calcium and phosphorus to lesser degrees, and decreased his magnesium retention.

The study reported by Slater (1961) compared mineral balances over observation periods of two to three days from the sixth to ninth days of life. They compared the balances in 13 breast-fed infants and 9 infants fed cows' milk formula (containing 317 IU vitamin D/400 ml reconstituted dried milk). The ratios of mineral retention for the breast-fed infants to bottle-fed infants were:

	Breast-fed/Bottle-fed
Mg	1/3–4
Ca	1/5
P	1/3

When additional phosphorus (120 mg/day) was given to the breast-fed infants, their urinary excretion of calcium dropped from the normal for breast-fed infants (4.43 ± 2.4 mg/kg/24 hr) to 2.07, close to that of bottle-fed babies (2.40). Their urinary phosphorus increased from 0.46 to 20 mg/kg/24 hr, but was still less than that put out by bottle-fed infants (34.9 mg/kg/24 hr). Their urinary magnesium dropped substantially from 0.61 to 0.19 mg/kg/24 hr (less than that on cows' milk: 34.9). The fecal output was not measured.

Despite the better retention of these minerals by infants on cows' milk as compared with that of breast-fed infants, it is among formula-fed infants that symptomatic hypocalcemia (often with hypomagnesemia) constitutes a problem. Thus, subsequent studies have been done with cows' milk adapted to resemble mothers' milk more closely. Widdowson (1965) compared mineral retentions by infants fed human and adapted cows' milk (Table 4-4). She observed several striking differences in retentions. Most notable was the low calcium retention during the fifth to seventh days of life in the formula-fed infants, as compared with that of breast-fed infants. By the fourth to seventh weeks, the calcium retention was greater in infants on one of the formulas and less in those on the formula that, paradoxically, delivered the greatest amount of calcium, than it was in the breast-fed infants. The phosphorus retentions were greater in all of the formula-fed infants than in the breast-fed infants, and the magnesium retentions of the formula-fed infants were the same or

TABLE 4-4. Magnesium, Calcium, and Phosphorus Retention in Infants Fed Human and Adapted Cows' Milk[a]

	Content			Mg		Ca		P	
	Mg	Ca	P	5–7 days	4–6 wk	5–7 days	4–6 wk	5–7 days	4–6 wk
Breast milk	mg/100 ml			Mean ± S.D. or mean and range: mg/kg/day					
5–7 days	3.2	30.7	16.6		2.7		23.7		16.8
4–6 wk	3.3	28.8	14.2	1.9 ± 1.0	(1.3–4.6)	19.6 ± 6.1	(22.9–24.6)	20.6 ± 6.1	(13.3–21.1)
Formula 1[b]	5.0	48.1	35.6	2.4 ± 1.1	2.4	4.1 ± 11.4	31.7	27.8 ± 4.8	28.7
					(0.2–3.9)		(12.5–46.0)		(26.1–36.9)
Formula 2[b]	6.3	63.2	48.2	3.1 ± 0.6	4.2	4.7 ± 8.2	12.9	34.0 ± 5.8	29.9
					(2.0–6.0)		(2.3–27.7)		(19.7–38.1)

[a] Data from Widdowson (1965).
[b] With vitamin supplements in milk.

greater than those of the breast-fed infants. This study confirmed, by showing the poor retention of calcium by the young neonate on cows' milk, the greater susceptibility of infants fed cows' milk than breast-fed infants to calcium insufficiency. The high content of phosphorus and saturated fats of cows' milk has each been implicated in the hypocalcemia (Oppé and Redstone, 1968; Widdowson, 1969; Barltrop and Oppé, 1970; Pierson and Crawford, 1972) but each of these factors would also cause interference with retention of magnesium.

4.3.1.2. Serum Magnesium, Calcium, and Phosphorus Levels in Infants Fed Cows' and Human Milk

Hyperphosphatemia, and a wider than normal range of serum calcium levels are frequently encountered in normal infants fed cows' milk formulas from birth, abnormalities that are in contrast to ranges within normal limits in most normal breast-fed infants. Studies of comparative serum calcium and phosphorus values in normal infants were undertaken when it was found that infants with neonatal tetany had hypocalcemia and hyperphosphatemia and that this syndrome was virtually unknown where breast-feeding was customary. Bakwin (1937) considered the high phosphorus content of cows' milk to be contributory to persistent neonatal hyperphosphatemia, which he believed might be intensified by transient hypoparathyroidism, such as had been proposed by Pincus and Gittleman (1936) to explain nonrachitic tetany in a 7-week-old infant. They found that feeding infants phosphate solutions resulted in just such a rise in serum phosphorus and fall in serum calcium as is seen in neonatal tetany. Immaturity of the kidneys, with inability to clear phosphate at normal (adult) rates, was proposed by Dean and McCance (1948). Both theories have been substantiated, although new insights have recently been acquired.

L. Gardner *et al.* (1950) studied 16 cases of tetany that provided support for the etiologic role of the high P/Ca ratio of cows' milk (which all 16 infants with tetany had been fed). They also showed that the maximum renal P clearance of the infants was only 10% of the probable glomerular filtration rate [shown to be less

than half that of adults (Dean and McCance, 1947)]. This they attributed to prenatal factors, such as maternal hyperparathyroidism with secondary neonatal hypoparathyroidism. They also considered serum magnesium levels in normal infants on different feedings, in an attempt to elucidate the cause of neonatal tetany, and showed that even normal newborn infants on formula had pronounced falls in total serum magnesium that were accompanied by decreased ionized calcium and increased serum phosphorus levels. A premature infant shifted from human to cows' milk promptly exhibited a rise in serum P from 6.45 to 11.26 mg/100 ml, that dropped to the original level several days after reinstituting human milk feeding.

The studies of Oppé *et al.* considered only the serum calcium and phosphorus levels of bottle-fed and breast-fed infants and confirmed that the latter had significantly lower serum phosphorus and higher serum calcium levels than the former (Oppé and Redstone, 1968). Infants fed cows' milk adapted to resemble breast milk had the same mean serum calcium levels as did breast-fed infants although there were more with hypercalcemia and several with marginal hypocalcemia, not seen in the infants on breast milk (Fig. 4-15A). The lowest range of serum phosphorus levels was in the breast-fed infants; that in adapted cows' milk was lower than in unadapted cows' milk, but higher than levels in breast-fed infants (Fig. 4-15B). These investigators commented that early addition of cereals (with their high phosphorus as phytate content) to the infants' diets can increase the tendency toward hypocalcemia. It should be noted that phytates also interfere with absorption of

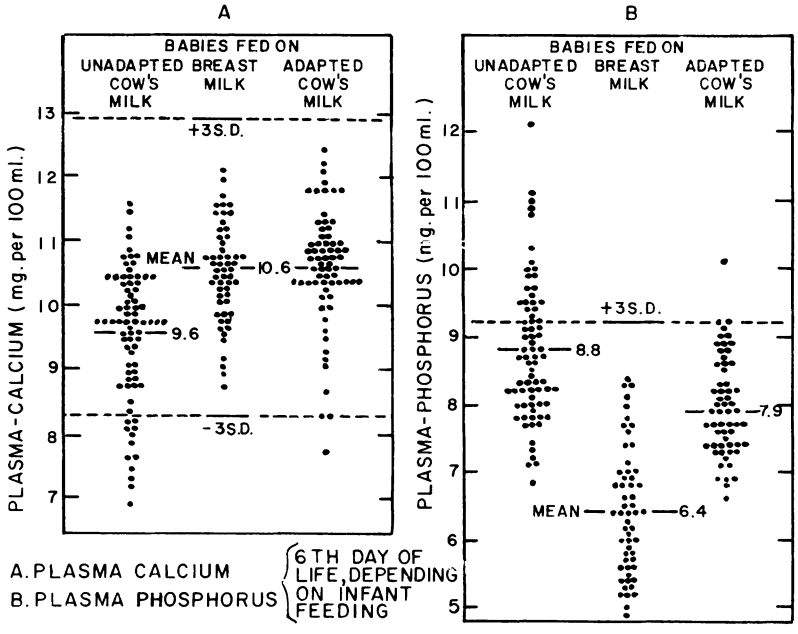

FIGURE 4-15. Plasma calcium and phosphorus in babies fed breast milk or cows'milk. (From TE Oppé and D Redstone: *Lancet* 1:1045–1048, 1968.)

magnesium. Two years later, this group published its further studies of the factor(s) in cows' milk responsible for the induction of infantile hypocalcemia, resulting in the symptomatic neonatal tetany that is seen, usually by the fifth to seventh days of life of formula-fed normal-birth-weight infants (Barltrop and Oppé, 1970). They used milk preparations with altered calcium and phosphorus contents, and found that neither is solely responsible for the hypocalcemia. They considered the ratio of dietary Ca/P most important. Addition of calcium to cows' milk formula fed to low-birth-weight infants increased their calcium retention (Barltrop and Oppé, 1973). Feeding low-birth-weight infants (4–41 days of age) formulas differing in calcium and phosphate contents exerted little influence on the plasma calcium and phosphorus levels, which varied widely (Barltrop *et al.*, 1977). The investigators commented that additional factors (than calcium, phosphorus, and fat contents of the formula) require study. They did not explore the magnesium levels; all of the cows' milk formulas used incorporated vitamin supplements (Widdowson, 1965).

The effect of vitamin D on the serum calcium and phosphorus levels of infants fed cows' milk or breast milk was studied by Pincus *et al.* (1954). They analyzed the levels on the day after birth and on the fifth day of life (Figs. 4-16A, B). All of the infants on cows' milk had significantly higher serum phosphorus levels on day 5 than did the breast-fed infants, whether or not they were given vitamin D. They observed that administration of vitamin D to formula-fed infants, in the first five days of life, increased the incidence of hypocalcemia (below 8 mg/100 ml) from 10.9% in infants without vitamin D to 17.3% of those who were given vitamin-D-fortified milk (400 USP units/quart), and to 30% of those given nonfortified milk, but a higher dose of vitamin D (600 units daily in an aqueous preparation of multivitamins). This finding is in accord with the later observation that 5- to 7-day-old infants on cows' milk retained little calcium (4.1–4.7 mg/kg/day) as compared with that of breast-fed 5- to 7-day-old infants (19.6 mg/kg/day) who were given no vitamin supplements (Widdowson, 1965). Breast-fed infants, given the same vitamin preparation, exhibited no such change in calcium levels (Pincus *et al.*, 1954). This group later showed that vitamin D also played a role in neonatal hypomagnesemia of formula-fed infants (Gittlemen *et al.*, 1964). They found that the serum magnesium levels of neonatal infants dropped minimally after five days of cows' milk formula, without vitamin D added, in contrast to the slight rise in serum magnesium of breast-fed infants. Adminstration of 600 units of vitamin D resulted in lower serum magnesium levels (from means of 1.75 to 1.5 mEq/liter on day 5) in the bottle-fed infants, but no change in infants on mothers' milk. Serum phosphorus levels rose by day 5 in bottle-fed infants, with our without vitamin D, but did not rise in any of the breast-fed babies.

In the study of normal neonatal infants by Gardner *et al.* (1950) that showed increased serum phosphorus and decreased total magnesium and ionized calcium in those that were on formula, each bottle-fed newborn infant was given 750 units of vitamin D_3, whereas the breast-fed infants received no vitamin supplements.

Anast (1964) studied serum magnesium levels in a large group (72) of normal full-term infants who were born without complications after normal pregnancies. Almost half (34) were breast-fed and received no vitamins; the remainder (38) were given evaporated milk formulas containing 400 units of vitamin D. He found the

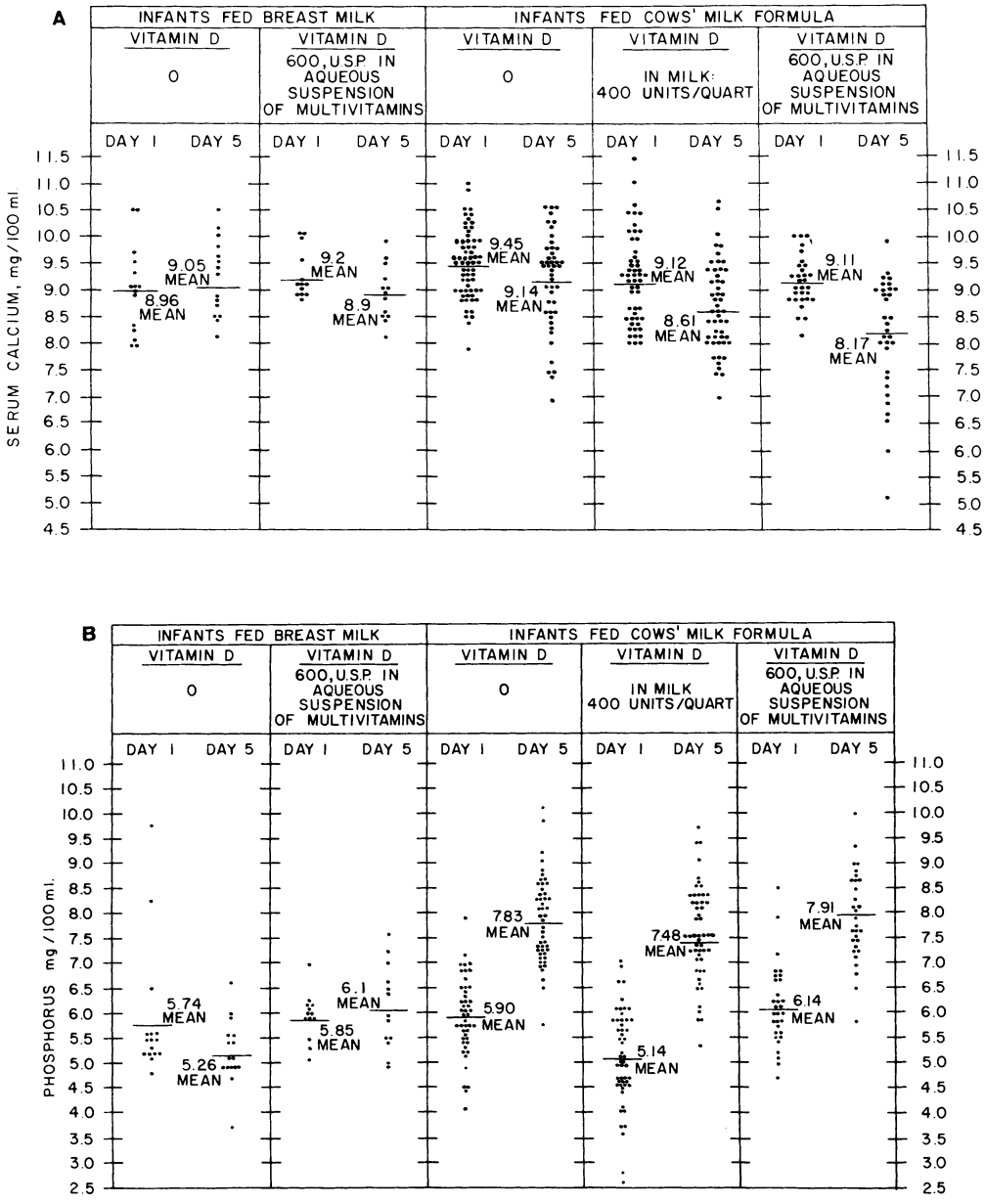

FIGURE 4-16. Serum calcium (A) and phosphorus (B) levels in infants fed breast milk or cows' milk without and with vitamin D supplements. (Adapted from Pincus *et al.*, 1954.)

mean serum magnesium levels of bottle-fed babies to be lower than that of breast-fed babies on days 3–5, and attributed the difference to the high phosphorus content of cows' milk. In a smaller study (22 formula-fed infants and 5 breast-fed infants) no difference was found in serum magnesium values (Bajpai *et al.*, 1966).

In contrast, Ferlazzo *et al.* (1965) found that breast-fed infants had slightly lower serum magnesium levels (1.5 mEq/liter) than did infants given half-cream cows' milk (1.7 mEq/liter). They speculated that this difference might reflect maternal hypomagnesemia.

Plasma calcium, magnesium, and phosphorus levels of bottle-fed and breast-fed infants were compared by Harvey *et al.* (1970). Among normal formula-fed infants, the mean plasma phosphate level was 8.25 mg/100 ml, with levels reaching as high as 21, as compared to a mean of 6.25 in breast-fed infants, none of whom had plasma P above 9.8 mg/100 ml. The plasma magnesium levels were significantly lower ($p \leq 0.001$) on the sixth day of life in the bottle-fed infants than in breast-fed infants. At that time the mean levels of magnesium were 0.91 mEq/liter and 1.33 mEq/liter, respectively, and the mean levels of calcium were 7.6 and 8.6 mg/100 ml for normal bottle-fed and breast-fed babies. The ranges of levels were wider in bottle- than breast-fed infants.

	Bottle-fed	Breast-fed
Plasma Mg (mEq/liter)	0.67–1.6	1.0–1.7
Plasma Ca (mg/100 ml)	3.8–11.2	8.0–12.4
Plasma P (mg/100 ml)	4.6–21.0	4.1–9.8

Convulsing infants in this study had mean plasma magnesium levels lower than did breast-fed infants, but equal to levels of bottle-fed infants (0.9 mEq/liter). Their mean serum calcium level (6.3 mg/100 ml), however, was lower than that of bottle-fed normal infants (7.6 mg/100 ml). Snodgrass *et al.* (1973) also observed a greater rise in serum magnesium and calcium levels from the first day of life to days 6–8 in breast-fed versus formula-fed infants.

Forfar *et al.* (1971/1973) reported that normal, breast-fed infants had serum magnesium levels on the sixth day of life that equaled that in cord blood, whereas those on cows' milk showed a decline in serum magnesium levels during the second to sixth days. Convulsions of infancy that occurred from the fourth day onward in 62% of the infants, were associated with plasma magnesium concentrations below the normal range in 65% of the cases. There was a strong positive correlation between magnesium and calcium levels ($p \leq 0.001$) and a lesser but still significant negative correlation between magnesium and phosphorus levels ($p \leq 0.01$). In a study of 75 additional consecutive newborn infants with convulsions, these investigators observed that all of the convulsing infants were fed an evaporated milk formula (Cockburn *et al.*, 1973). Figure 4-3 depicts the comparative values for plasma calcium, magnesium, and phosphorus concentrations for (normal) breast-fed infants and for the infants with convulsions. They also found that both mean plasma values and ranges for these elements differed significantly in breast-milk and normal cows'-milk-fed infants, particularly on the fifth to seventh days of life. They considered the possibilities, suggested in the literature, that the high phosphorus

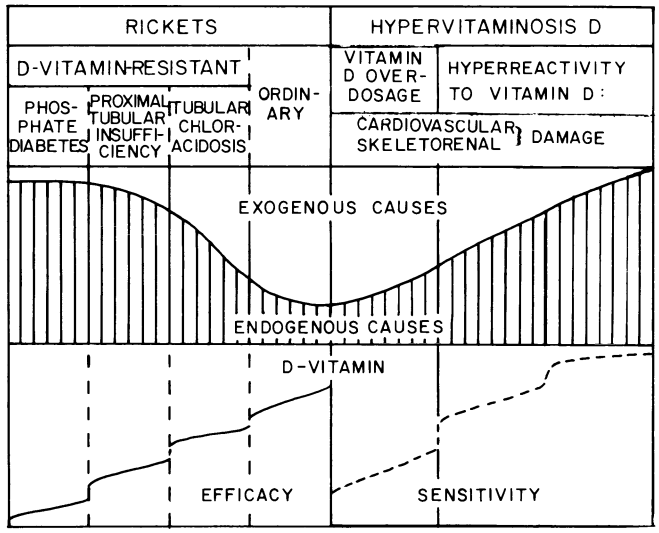

FIGURE 4-17. Spectrum of reactions to vitamin D. (Adapted from Fanconi, 1956.)

load provided by cows' milk might exert a hypocalcemic effect mediated by transient hypoparathyroidism (Fanconi and Prader, 1967), maternal calcium or vitamin D deficiency (Watney *et al.*, 1971) or either vitamin D administration (Gittlemen *et al.*, 1964), or deficiency (Barr and Forfar, 1969) in the infant. They noted that infantile hypomagnesemia similarly might result from the disproportionate phosphorus load, mediated by transient hypoparathyroidism. The better response to magnesium than to calcium therapy of neonatal tetany, and the risk of aggravating the hypomagnesemic convulsive state was also noted. This may constitute reconsideration of an earlier recommendation that the hypercalcemic agent, vitamin D, be given in high doses (5000 IU/day) in the treatment of hyperphosphatemic (hypocalcemic) tetany of the newborn (Barr and Forfar, 1969). It is noteworthy that comments have been made in textbooks that vitamin D is ineffective in transient neonatal tetany (Nelson, 1964) and might be dangerous (Fourman and Royer, 1968).

That accepted prophylactic doses of vitamin D can lower the serum magnesium levels of normal infants, though only slightly, is an observation that should be considered in light of the findings that (1) vitamin D excess causes magnesium loss; (2) there is a broad spectrum of reactivity to vitamin D (Fig. 4-17, Fanconi, 1956) (Reviews: Seelig, 1969b, 1970a,b), and that fortification of milk and other foods makes intakes of higher than prophylactic amounts almost unavoidable. It is possible that such high intakes of vitamin D in infancy, when phosphate intakes are also likely to be high (in bottle-fed babies) and there is risk of magnesium deficiency, can contribute not only to the acute infantile manifestations of abnormal calcium and magnesium homeostasis, but to early and later cardiovascular skeletal, and renal, diseases (Seelig and Haddy, 1976/1980).

4.3.2. Risks of Excessive Vitamin D in Infancy

There is wide variation in susceptibility to vitamin D toxicity and in the requirements for vitamin D, both in experimental animals and in man (review: Seelig, 1969b). Thus, whether infants will develop early or late sequellae of hypervitaminosis D depends upon their tolerance of the therapeutic amounts of vitamin D most ingest for prophylaxis of rickets. The Food and Nutrition Board of the American National Research Council (1968 Edition) commented that normal full-term infants require as little as 100 IU of vitamin D daily to prevent rickets and that premature infants usually require no more than 200 IU. As a result of the outbreak in Great Britain of infantile hypercalcemia, with resultant supravalvular aortic stenosis syndrome (SASS), comprising arterial as well as valvular lesions, renal damage, growth failure, a typical peculiar facies, and severe mental retardation which resembles that reported by Williams *et al.* (1961) (Reviews: Black, 1964; Seelig, 1969b) (Fig. 4-18), there was intensive reevaluation of the possible causative role of hypervitaminosis D. A Committee of the British Paediatric Association reported that the intakes of vitamin D by British infants might well reach 4,000 IU daily if all of the available fortified infant foods and supplements were consumed (Committee Report, 1956)—this despite their earlier (1943) cited recommendation that the total daily intake of vitamin D should not exceed 500–700 units. There was also an outbreak of the SASS and other outflow obstructions (Fig. 4-19) in Germany where

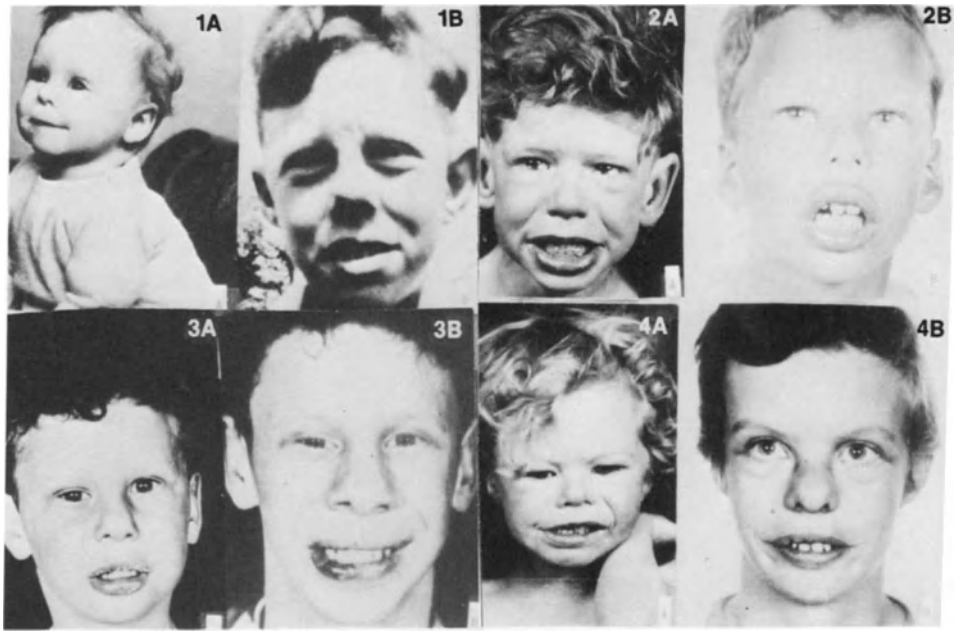

FIGURE 4-18. Four English survivors of "idiopathic" infantile hypercalcemia, attributed to moderately high vitamin D intakes. Pictures at earlier (A) and later (B) age. (Courtesy of JA Black.)

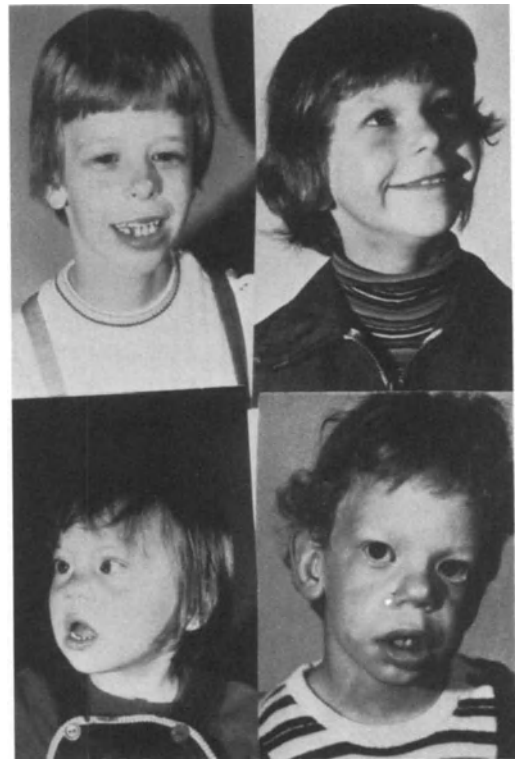

FIGURE 4-19. German children with SASS ± pulmonary arterial stenosis, mental retardation, and cardiofacies: Survivors of high dosage vitamin D (Stosstherapie). (Courtesy of Beuren.)

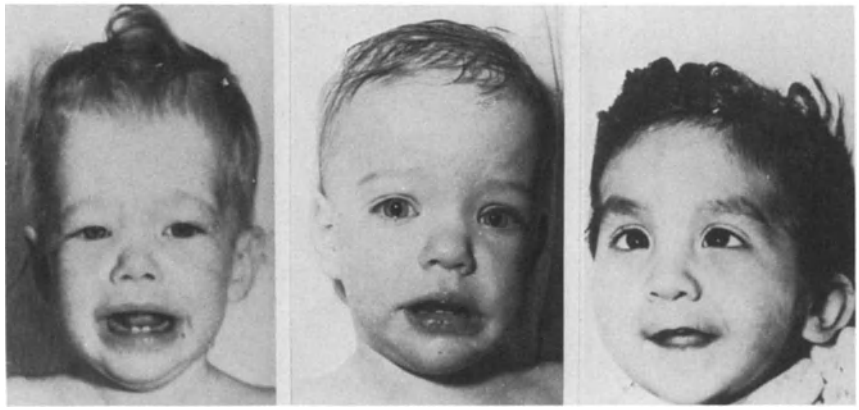

FIGURE 4-20. Infants with infantile hypercalcemia: U.S.A. Vitamin D intakes: 500–1,000 IU day. (From D O'Brien *et al.: JAMA* 173:1106–1110, 1960.)

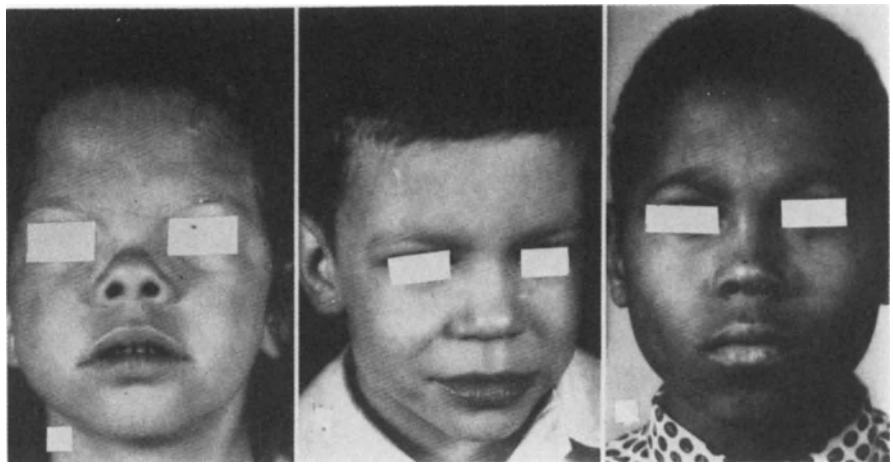

FIGURE 4-21. Children with supravalvular aortic stenosis with and without cardiofacies and mental retardation: U.S.A. (From OE Ottesen *et al.: Radiology* 86:430–435, 1966.)

extremely high doses (Stosstherapie: 200,000–300,000 units) were injected two or three times a year (Beuren *et al.*, 1964, 1966). Even in the United States, where the American Medical Association Council on Food and Nutrition had refused to countenance more than 400 IU vitamin D per quart of milk (F. Bing, 1941), many cases have been reported (Seelig, 1969b) (Figs. 4-20–4-22) that are indistinguishable from those associated with moderate to extreme overdosage with vitamin D. Classic SASS, originally described only in fair-skinned children (Williams *et al.*, 1961; Seelig, 1969b), has also been reported in black children (Kostis and Moghadem, 1970; Fig. 4-22). Cardiac outflow abnromalities, whether as the entire complex of SASS,

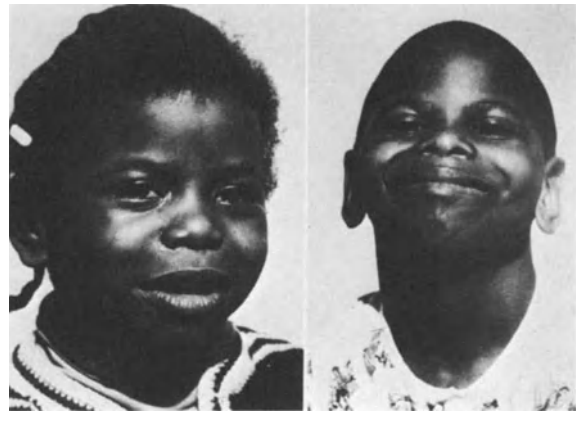

FIGURE 4-22. American children with SASS. Girl, eleventh child of 43-year-old mother; boy, fourth child of 21-year-old mother. (From JB Kostis and AN Moghadem: *Chest* 57:253–258, 1970.)

as an incomplete picture (Fig. 4-21) with stenosis of the right outflow of the heart with or without notable mental retardation and/or cardiofacies (Figs. 4-23, 4-24, 4-25), or as part of a more generalized picture of "congenital" cardiovascular disease is now so prevalent that the literature is replete with papers describing individual or familial instances, diagnostic procedures, and techniques for surgical repair. This complex of diseases had been so rare before the 1930s as to have been omitted or given only passing reference in most textbooks and atlases of cardiovascular pathology (Perou, 1961). Congential disorders associated with an exogenous etiologic factor (as the thalidomide-induced teratology), are characterized by a wide range of malformations, depending on the magnitude, time, and extent of the insult (Taussig, 1965, 1966; Beuren *et al.,* 1966). Thus, one should anticipate a similar variety of abnormalities associated with the damage caused by the nutritional imbalances that are part of the hypervitaminosis-D-complex (Taussig, 1965, 1966). That such a variety is likely to exist is indicated by the different findings reported in victims of hypervitaminosis D and in relatives. Multiple arterial stenoses were described in infants who died early with severe infantile hypercalcemia (Bonham-Carter and Sutcliffe, 1964), and coexisting bilateral pulmonary artery stenosis, as well as additional cardiovascular abnormalities, depending on the degree and time of vitamin D overdosage. The mental and facial abnormalities were not consistent. In a particularly interesting family with 11 cases, nine of whom had supravalvular aortic stenosis without cardiofacial appearance and mental retardation, two died in infancy with generally hypoplastic major arteries before the aortic stenosis had developed. One died at seven months after unsuccessful attempts to control his infantile tetany with dihydrotachysterol (0.6 mg/day) and vitamin D (1,000 1U/day) had failed, despite hypercalcemic response shortly before death. His cousin died suddenly at three

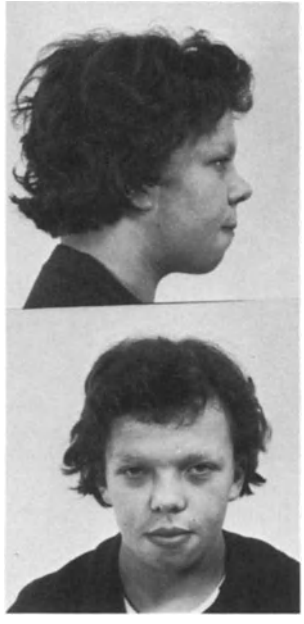

FIGURE 4-23. Finnish girl with supravalvular pulmonic stenosis, cardiofacies, and mental retardation. From G Härtel *et al.: Am Heart J* 75:540–544, 1968.)

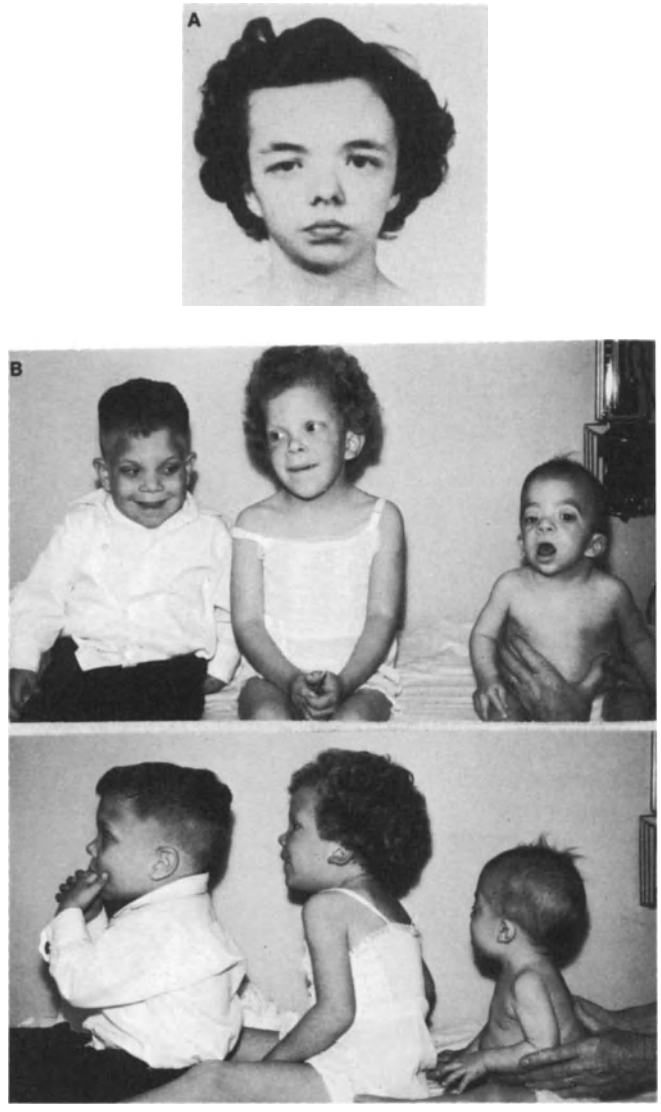

FIGURE 4-24. American children with pulmonary valvular dysplasia and stenosis, with cardiofacies, growth retardation, chest deformation, and other cardiac abnormalities. [From JA Noonan, *Am J Dis Child* 116:373–380, 1968 (A) and LM Linde *et al.: Brit Heart J* 35:301–304, 1973 (B). Courtesy of Linde, 1979.]

weeks of age, a week after a vitamin D treatment (Beuren *et al.*, 1966). This paper dealt with 54 patients, in most of whom there was a clear history of "Stosstherapie." Several of the mothers also admitted to continuous vitamin D supplementation during pregnancy. Occurrence in one family of instances of sudden infant death, hypercalcemia, hyperreactivity to vitamin D, and a wide range of cardiovascular stenotic and hypoplastic pathologic changes, with and without peculiar facies and mental retardation, suggests a common pathogenesis. In the family reported by

FIGURE 4-25. American siblings with pulmonary valvular dysplasia with cardiofacies and growth retardation (girl) and without (boy). (From ED Koretsky *et al.: Circulation* 40:43–54, 1969; courtesy of Moller, 1979.)

Beuren *et al.* (1966) and in isolated unrelated and other familial cases, there was strong circumstantial evidence that those who developed the syndrome were unable to detoxify the excessive parenteral doses of vitamin D that was a common mode of prophylaxis against rickets in Germany at that time.

The similarity to the SASS of the syndrome, seen in England among survivors of infantile hypercalcemia (Schlesinger *et al.*, 1956, Black and Bonham-Carter, 1963), suggested that some infants were so susceptible to vitamin D toxicity that ingestion of lesser amounts could cause permanent injury. Taussig (1965, 1966) hypothesized that hyperreactivity to vitamin D might well be the cause of the "congenital" heart disease: SAS, and of gradations of injury. Because hypercholesterolemia was found in some of the hypercalcemic infants, she speculated that hyperreactivity to vitamin D might be contributory to hypercholesterolemia in countries where vitamin D supplementation of foods is widespread (Taussig, 1965, 1966). There has been experimental and epidemiologic evidence that even moderately increased vitamin D intakes have increased blood cholesterol levels (Feenstra and Wilkins, 1965; Dalderup *et al.*, 1965; Linden, 1974b, 1975/1977; Linden and Seelig, 1975). Hypertenson is also seen in vitamin D toxicity and in children with the SASS.

It should be remembered that the addition of 400 IU to each quart of milk is an amount arrived at empirically, because that amount of vitamin D delivered in milk was more effective in curing rickets than the same amount in oil (Reviews: Seelig, 1969b, 1970). The American Academy of Pediatrics expressed concern about the total vitamin D consumption in the United States, which they calculated might range from 600 to 4,000 IU daily from marketed fortified products (Committee Report, 1963). They recommended that no more than 400 IU should be provided from all sources, including sunlight, and reiterated and amplified their concern about hypervitaminosis D two years later, stressing the possible role of maternal factors (Committee Report, 1965). In consultation with the Committee, D. Fraser (1967) wrote a report reaffirming the limitation of vitamin D to no more than 400 IU/day, and referred to evidence that as little as 100 IU or less has protected against

rickets (Drake, 1937; Glaser *et al.*, 1949). Despite these official recommendations, fortification of many foods with vitamin D persists, and many Americans supplement their diets with vitamin-D-containing vitamin preparations. Studies of dietary intakes show that, both in Canada and the United States, vitamin D intakes are often excessive (Dale and Lowenberg, 1967; Broadfoot *et al.*, 1972). A Canadian study of 1,000 children one week to five and a half years of age showed that 70% ingested more than 400 IU daily and 31% more than 1,000 IU daily (Broadfoot *et al.*, 1972). The narrow toxic/therapeutic ratio for vitamin D in infants (Stewart *et al.*, 1964), and the wide differences in the amounts of vitamin D that are required or can be tolerated support D. Fraser's (1967) call for reappraisal of national policies concerning vitamin D requirements. He referred to the known toxicity of vitamin D and to the lack of knowledge concerning possible long-term effects of intakes from infancy that exceed requirements severalfold.

It is possible that the increased incidence, since the 1930s, of children's diseases that used to be rare and that have characteristics that resemble those seen in vitamin D toxicity might be consequences of the concomitant widespread and sometimes intensive use of vitamin D. The profound changes in the pediatric picture, in the twenty-odd-year period from early in the 1930s to 1965, led Hutchison (1955) to raise the point " . . . it is just possible that the very measures which we have used to abolish rickets from the land may have resulted in the appearance of hypercalcemia in some susceptible infants." The new diseases he cited were infantile hypercalcemia, infantile renal tubular acidosis and fibrocystic disease of the pancreas, usually with marasmus and steatorrhea, and cystinosis. The first two of these disorders have been definitely correlated with overdosage or hyperreactivity to vitamin D (Fig. 4-26, Lightwood and Butler, 1963; Review: Seelig, 1969b). Renal

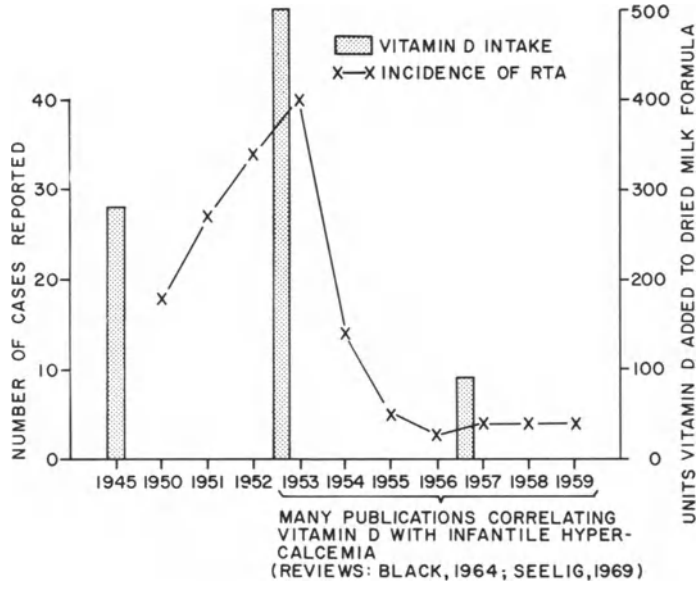

FIGURE 4-26. Correlation of renal tubular acidosis with vitamin D fortification of infant formula. (Adapted from Lightwood and Butler, 1963.)

sclerosis and skull and other bone deformities are common in victims of SASS (Seelig, 1969b), and skeletal abnormalities are also seen in other outflow obstructive disease, such as of pulmonary stenosis (Noonan, 1968; Linde *et al.*, 1973). It is of interest that congenital valve disease is not uncommon in osteogenesis imperfecta. It has been suggested that mucoviscidosis might also be a consequence of hypervitaminosis D (Coleman, 1965). To what extent magnesium loss caused by excess vitamin D might contribute to sequellae of infantile hypercalcemia is not certain.

Moncrieff and Chance (1969) have pointed out that the margin between the therapeutic and the toxic dose of vitamin D is narrow, and described small calcium deposits in renal biopsy specimens of four children with hyphosphatemic rickets. Hypophosphatemic rickets, which had initially been treated with massive doses of vitamin D, was found to be associated with hypomagnesemia (0.5 and 0.7 mEq/liter) in a five-year-old boy and a two-year-old girl (Reddy and Sivakumar, 1974). Despite concomitant hypocalcemia, there had been no convulsions. Magnesium therapy caused correction of the mineral abnormalities in the serum. It is possible that the latter two young children also had early renal damage, such as Moncrieff and Chance (1969) described, that resulted in renal wasting of magnesium. It has also been postulated that, since conversion of vitamin D to its active metabolites involves magnesium-dependent enzymatic steps, vitamin-D-resistant rickets might be a consequence of decreased formation of the active metabolities as a result of magnesium deficiency (Rösler and Rabinowitz, 1973). In the 13-year-old girl, whose magnesium-responsive vitamin-D-resistant rickets was hyperphosphatemic, PTH administration produced phosphaturia, but did not correct her symptomatic hypocalcemia until her hypomagnesemia (0.5 mEq/liter) was treated (Rösler and Rabinowitz, 1973). Thus, in this child with idiopathic hypoparathyroidism, magnesium depletion might have been primary, and causative of impaired bone response to PTH. Whether the children with hypophosphatemic vitamin-D-resistant rickets reflect an overt hyperparathyroidism secondary to hypomagnesemia is a possibility that deserves consideration. If the abnormal response to vitamin D is secondary to magnesium deficiency, attempting to treat the condition by this agent, which increases magnesium loss, can be responsible for damage that may not be manifest immediately. Since magnesium deficiency has been shown to cause osteoporosis in experimental animals, the osteopenia of vitamin-D-resistant rickets might be mediated in part by magnesium deficiency. The excess vitamin D given in the face of the magnesium deficiency, which in itself causes renal and cardiovascular damage, can intensify those lesions.

The cardiovascular lesions (that are related to the SASS) that cause death in earlier infancy from coronary or generalized arteriosclerosis, or that might be the pediatric precursors of adult atherosclerosis, might well be the result of nutritional and hormonal imbalances, to which vitamin D excess contributes. It is of interest to note that it was at the beginning of the era referred to by Hutchison (1955) as being marked by the emergence of new pediatric diseases, that Lightwood (1932) suspected hyperreactivity to vitamin D as a possible etiologic factor in the first published case of what was probably a late form of severe infantile hypercalcemia. He described a retarded, dwarfed two-year old girl who died with widespread endarteritis obliterans; endocardial calcification, hypertension, calcerous renal

tubular casts, and osteosclerosis. In 1956, as chairman of a committee of the British Pediatric Association assigned to investigate the relationship of vitamin D (added to milk and other infant foods) to the virtual epidemic of infantile hypercalcemia, he recommended that the amount of vitamin D given to infants be sharply reduced, the maximum amount permitted, from all sources, to be determined after further investigation. That investigation is yet to be undertaken.

4.4. Primary Malabsorption of Magnesium

The first infant, whose primary hypomagnesemia and secondary hypocalcemia was associated with convulsions that were responsive only to magensium, was found to have isolated intestinal malabsorption of magnesium (Paunier *et al.* 1965, 1968b). Even with about five times the normal oral intake of magnesium, this boy's serum magnesium levels remained at 1.1–1.4 mEq/liter. On discontinuing the supplement for a few days at 10, 18, and 30 months of age, there were further decreases in serum magnesium levels. PTH administration caused hypercalcemia without affecting the serum magnesium; large doses of vitamin D also increased the calcium level, but caused a gradual fall in serum magnesium, even when the infant received magnesium supplements. Magnesium malabsorption has persisted throughout the eight years of observation; interrelationships of his chronic magnesium deficiency with PTH were then evaluated (Suh *et al.*, 1973).

The second patient with this abnormality was reported by Salet *et al.*, (1966). They identified isolated malabsorption of magnesium, but normal renal magnesium conservation. They considered the condition congenital and later reported it to be a familial cause of primary hypomagnesemia, when a new sibling was found to have the same disorder (Salet *et al.*, 1970). Like the first infant (Paunier *et al.*, 1965, 1968b), this child responded to exogenous PTH by increased serum calcium but not change in serum magnesium (Salet *et al.*, 1966). Initially, his urinary output of phosphorus had been very low, and he had hyperphosphatemia. High-dosage vitamin D caused hypercalcemia and increased magnesium requirements. Magnesium therapy corrected the hypocalcemia and hypomagnesemia, and lowered the serum phosphorus level.

Infantile hypomagnesemia, as a result of malabsorption of magnesium (but normal renal conservation of magnesium) was reported in a boy born to first cousins, suggesting that this might be an hereditary disease with recessive genetic characteristics (M. Friedman *et al.*, 1967). This infant's convulsions began on the 23rd day of life, were intensified by calcium therapy and subsided, as did his irritability and twitching, following parenteral magnesium therapy. Metabolic balance studies showed that he required over 600 mg of magnesium daily to sustain positive magnesium and calcium balances.

The cited cases were in French-Canadian (Paunier *et al.* 1965, 1968b), French (Salet *et al.* 1966, 1970), and Indian (M. Friedman *et al.* 1967) male infants. A Norwegian male infant with comparable manifestations was reported by Skyberg *et al.* (1967, 1968). As in the other cases, despite large-dosage oral magnesium supplementation, the infant's serum magnesium levels remained subnormal, 1.3–1.4 mEq/

liter, and fell further on temporary discontinuation of the supplements. PTH exerted no effect on the low serum magnesium, but raised serum calcium and increased phosphaturia twofold, during a short period in which magnesium supplements were withheld. Identification of the same disorder in two Norwegian brothers by the same group of investigators (Stromme *et al.*, 1969) led them to term the condition "familial hypomagnesemia." The first of the brothers had died at 50 days of life, with continuous seizures associated with hypocalcemia that had been unresponsive to intravenous calcium or to vitamin D or anticonvulsive therapy. No magnesium determinations had been performed. When the second brother developed convulsions the third week of life, hypomagnesemia was identified. His hypocalcemia and slight hyperphosphatemia, as well as his seizures, subsided in response to intravenous magnesium administration. His serum magnesium remained subnormal (1.1–1.4 mEq/liter) while receiving high-dosage oral magnesium supplementation. On its temporary discontinuation, he again gradually developed severe hypomagnesemia.

A Swedish female infant, who developed convulsions at two months of age, had hypomagnesemia, hypocalcemia, peripheral edema, and bulging fontanelles on admission (Haijamae and MacDowall, 1972). She required continuous high dosage oral magnesium supplements. After withdrawal of the magnesium supplements, her serum magnesium dropped from 1.3 to 0.5 mEq/liter, and her serum phosphorus rose from 4.8 to 6.0 mg/100 ml. Serum calcium rose and serum potassium fell slightly. More significant were the skeletal muscle electrolyte changes: Magnesium and potassium levels fell 9.5% and 7% respectively; muscle sodium rose by 53%.

Nordio *et al.* (1971) have intensively studied an Italian boy, who was hospitalized at seven months of age with convulsions and tetany that had not responded to oral calcium and vitamin D therapy. When he failed to improve following intravenous calcium, his plasma magnesium was measured and found to be 0.67 mEq/liter (normal range: 1.7–2.1). Hypoparathyroidism and possible magnesium deficiency were deemed likely, and he was given PTH and magnesium (2 g) intramuscularly, with partial improvement. He required high oral intakes of magnesium (30–70 mg/kg/day) to normalize his clinical picture, and to correct the abnormal electroencephalogram, electromyogram, and electrocardiogram as well as serum calcium and phosphorus. His plasma magnesium did not attain normal levels. Each time magnesium supplementation was stopped, there was recurrence of irritability and tetany. His tissue potassium/sodium ratio was found to be low. He had higher than normal sweat concentrations of magnesium, but normal erythrocyte and cerebrospinal fluid levels of magnesium. He was proved to have selective intestinal magnesium malabsorption; his kidneys were able to conserve magnesium when he had hypomagnesemia. His intestinal mucosal ATPase seemed normal when tested in a medium containing $MgSO_4$. Electron microscopic examination of his intestinal mucosal cells showed dilated endoplasmic reticulum and mitochondrial swelling in the apical portion of the cells. The brush border was normal. Long-term oral magnesium therapy prevented recurrence of the hypocalcemia, but his serum magnesium remained below the normal range, although not at the severely hypomagnesemic level found when he was seven months old. He was mentally retarded (I.Q. at 32 months was 68).

Woodard *et al.* (1972) reported diarrhea and anasarca as prominent manifesta-

tions that remitted with magnesium therapy in an American infant boy (two months old) whom they found to have selective magnesium malabsorption. Before detection of severe hypomagnesemia (0.06–0.1 mEq/liter), he had received calcium and anticonvulsant therapy for his generalized seizures, without improvement of either his hypocalcemia or his convulsions. Seizures abated after starting i.m. $MgSO_4$ therapy, and soon the diarrhea and edema cleared. To avoid recurrence of his seizures, the infant required more than 200 mg Mg daily, by mouth. His serum calcium had failed to rise in response to PTH while he was magnesium depleted; he developed a hypercalcemic response to its injection following magnesium repletion.

A Belgian boy, the ninth child of a mentally defective mother, was the fifth male sibling to have had convulsive attacks. Two brothers had died in the second and third months of life, respectively, having had generalized seizures; another had a single convulsion at six years of age, and a fourth had a seizure at 13 months (Vainsel *et al.*, 1970). The child, whose magnesium deficit was identified shortly before his death, had been hospitalized with convulsions, peripheral edema, and bulging fontanelles. He had constant tetany, bilateral Trousseau sign, and carpopedal spasm. He seemed unaware of his surroundings and, except for intensification in response to noise, did not respond to stimuli. He was given intravenous calcium on detection of hypocalcemia, which raised his serum calcium level from 6.15 to 8.5 mg/100 ml without improving the tetany. He had increased serum alkaline phosphatase, but normal phosphate levels. He was given high-dosage therapy of vitamin D (750,000 IU/week), which was stopped when hypomagnesemia was reported (0.4–0.65 mEq/liter). Parenteral therapy with magnesium was started, which raised his serum Mg to 2.3 mEq/liter. His tetany persisted until his death on the third day of the treatment with magnesium. Postmortem examination disclosed focal myocardial necrosis, calcinosis around a branch of a cerebral artery, and intimal calcification in another. Intraluminal calcium deposits were found in the proximal renal tubules and in the ascending limb of the loop of Henle. There was fibrosis and basement membrane proliferation in some glomeruli. He also had meningeal thickening and infiltration, a finding that had been reported in one of his brothers who had had seizures, and cerebral intimal calcification. A presumptive diagnosis of familial magnesium-malabsorption was made, on the basis of the similarity of the findings to those that had been described in the literature.

In retrospect, it seems likely that the boy (white American) with a history of similar manifestations—repeated convulsions, cyanotic attacks, tremors and nervousness from six months of age, for which he had been maintained on oral calcium and vitamin D supplement—might also have been a child with primary magnesium deficiency (J. F. Miller, 1944). He developed osteochondritis at 3½ years of age. When he was hospitalized (for malaria) at 6 years of age, and developed severe muscle cramps as well as carpopedal spasm and Trousseau sign, in the absence of hypocalcemia, he was found to have low serum magnesium (1.4 mEq/liter). All of his neuromuscular irritability subsided on oral magnesium supplementation; it recurred when treatment was stopped for a week. Marked hypomagnesemia, hypercalcemia, and hypophosphatemia were then observed, and again there was favorable response to oral magnesium therapy. Stromme *et al.* (1969) pointed out that this boy's early manifestations were similar to those of familial hypomagnesemia.

Another boy with osteochondrosis, who has renal magnesium wasting (Klingberg, 1970), has developed myocardiopathy and peripheral muscle weakness (Klingberg, personal communication), all of which fit the general picture of magnesium depletion. Whether his initial lesion might have been magnesium malabsorption, as seems probable in a patient reported in Vainsel *et al.* (1970), cannot be proved. It is plausible that his renal lesion and subsequent complications might have resulted from such a primary metabolic magnesium abnormality. Rapado *et al.* (1975) and Rapado and Castrillo (1976/1980a,b) have reported patients with chondrocalcinosis and renal calcinosis who had magnesium malabsorption.

It is of interest that calcium, vitamin D, and often PTH were used to control the neuromuscular irritability, associated with the first diagnosed hypocalcemia, in almost all of the cases cited. Their serum calcium rose, sometimes to hypercalcemic levels, as did their serum alkaline phosphatase. Their serum phosphorus levels dropped without improving the serum magnesium levels or the clinical signs, until their magnesium deficiency was diagnosed and corrected. Other children, who had histories of clinical signs suggestive of hypomagnesemic hypocalcemia, developed hypercalcemia when magnesium therapy was added to their high-dosage calcium and vitamin D therapy on which they were being maintained to control their hypocalcemia. These observations suggest that their release of PTH (Review: Anast, 1977), its conversion to an active form (Passer, 1976), or response to vitamin D may have been abnormal in the presence of hypomagnesemia. That magnesium therapy increases the calcemic response to vitamin D in hypoparathyroid patients has been recognized for many years.

Two of the infants described in this section were hypocalcemic, not responding to high-dosage vitamin D (Stromme *et al.*, 1969; Nordio *et al.*, 1971). Whether these infants had vitamin-D-resistant rickets that failed to respond to very high doses of vitamin D until their magnesium deficiency was repaired seems possible. Magnesium-dependent vitamin-D-resistant rickets has been described in a hypoparathyroid girl (Rösler and Rabinowitz, 1973) and in a rachitic boy (Reddy and Sivakumar, 1974), both of whose serum calcium levels rose and vitamin D requirements dropped substantially on correction of hypomagnesemia. It should be noted that the use of high doses of calcemic agents to raise the blood calcium of hypophosphatemic vitamin-D-resistant rickets (Moncrieff and Chance, 1969) or of other hypomagnesemic hypocalcemias can be nephrotoxic. Thus, evaluation of children with abnormal requirements or response to vitamin D for their magnesium status is indicated. Since vitamin D is necessary for the absorption of magnesium, children with abnormal vitamin D metabolism might have concomitant magnesium deficiency. Among those with hyperreactivity to vitamin D (Review: Seelig, 1969b), the excess magnesium loss (caused by hypervitaminosis D) can cause renal and cardiovascular damage directly, to which the vitamin D excess is contributory.

All but one of the affected infants were boys. In several of the families (Stromme *et al.*, 1969; Salet *et al.*, 1970; Bardier *et al.*, 1970; Vainsel *et al.*, 1970), more than one child was affected. In another (M. Friedman *et al.*, 1967) the parents were closely related. The genetics of abnormalities in magnesium intestinal absorption needs evaluation. Determination of the incidence of marginal magnesium deficiency in parents, siblings, and other close relatives of children with primary mag-

nesium malabsorption should be ascertained, as should possible relationships with abnormalities in vitamin D metabolism.

4.5. *Acute and Protracted Gastroenteritis in Infancy and Childhood*

Calculation of the amount of magnesium infants must retain daily (0.85 mEq) for normal growth and development and for their metabolic processes suggests that they have only a narrow margin of safety, assuming normal intestinal absorption (Harris and Wilkinson, 1971). Thus, infants are particularly subject to magnesium depletion when they have acute or protracted diarrhea. Breton *et al.* (1961), considering that the stool of infants with severe acute diarrhea contains an amount of magnesium almost equal to that ingested (Holt *et al.*, 1915), noted that the distribution of serum magnesium levels of such infants and of those with chronic diarrhea of mucoviscidosis did not differ substantially from that of normal infants. During recovery, however, the serum magnesium levels gradually fell, an observation that they considered suggestive of hemoconcentration during intestinal loss of fluid and of possibly transitory renal insufficiency, which masked the actual (tissue) deficit. In more severe gastroenteritis with refractory vomiting and diarrhea, severe hypomagnesemia has been reported (Back *et al.*, 1962). Among 5 infants (8 months to 2 years of age), with symptomatic hypomagnesemia associated with gastroenteritis, there were 3 with protein calorie malnutrition (*infra vide*) and 2 (1 and 2 years old, respectively) whose magnesium deficit seemed to be the result of the disturbance of the alimentary tract. Both infants improved on magnesium therapy, after i.v. fluids had proven ineffective and i.v. calcium had superimposed convulsions on the tetanic state. The authors noted the importance of magnesium in general cellular metabolism, and the observations of R. Fletcher *et al.* (1960) that repair of the deficit may improve impaired intestinal function. All 20 infants, who were severely dehydrated as a result of severe gastroenteritis and who had received intravenous therapy, developed one or more neurologic manifestations of magnesium deficiency (Back *et al.*, 1971/1973). Eleven had been well nourished before the acute episode; all recovered. Nine had been malnourished; 7 died. Of the 12 infants who developed neurologic signs only after intravenous therapy had been started, nine were being given additional potassium at the time. They reported that in their series of 20 children admitted with severe gastroenteritis all 20 developed neurologic signs and symptoms of magnesium deficiency, 75% while they were receiving potassium therapy. They stressed that it is important to correct both deficiencies, and found that when magnesium was given parenterally as magnesium sulfate (2 ml 25% solution) 15 of the 18 infants so treated responded with correction of their symptoms within 10 minutes; symptoms did not recur. Two had only partial response. One was also given calcium gluconate to control carpopedal spasm, but when the calcium was given again five hours later to control convulsions, it was ineffective; magnesium therapy controlled the convulsions.

Prolonged gastroenteritis in a three-month-old infant, starting a month after a

colostomy had been performed for intestinal obstruction, was followed by feeding full-strength vitamin-D-fortified cows' milk formula when the acute problem was corrected (Savage and McAdam, 1967). Clonic convulsions developed, which were found to be caused by hypomagnesemia (0.54 mEq/liter). The authors attributed the magnesium deficiency to a combination of factors: prolonged gastroenteritis (causing losses of magnesium and calcium), large feedings of full-strength cows' milk formula (replacing predominantly the calcium), and rapid growth during convalescence (increasing magnesium requirements). They cautioned that it might be unwise to give cows' milk to an infant recovering from severe diarrhea without first checking the magnesium and supplementing if indicated.

As in infantile severe diarrhea, which is accompanied by dehydration (Breton *et al.*, 1961; Paupe, 1971), the magnesium status of patients with cholera is difficult to evaluate and precarious. Kobayashi (1971) commented that muscle cramps and convulsions were often encountered during the rehydration phase, particularly in children, and in those given physiologic saline and sodium bicarbonate rather than lactated Ringer's solution. They reported that during the acute phase of the disease, hypermagnesemia (2.68–3.75 mEq/liter) was not uncommon, although patients under six years of age had mean levels of 2.68 mEq/liter ± 0.56.

Paupe (1971) reviewed the contribution of acute and chronic diarrhea in infancy and childhood to hypomagnesemia. He pointed out that such deficits might be missed, on measuring serum magnesium levels, because of the dehydration associated with loss of gastrointestinal fluids. On the other hand, failure to compensate for magnesium losses is likely explain the transitory and marginal hypomagnesemias reported during convalescence from acute diarrhea (Breton *et al.*, 1961; Bernal *et al.*, 1967). To avoid losses sufficient to be reflected by hypomagnesemia, Harris and Wilkinson (1971) administered magnesium salts to such infants empirically for many years with favorable results. They employed the procedure to determine magnesium depletion by ascertaining the percentage urinary retention of a parenteral load of magnesium, and showed that 20 to 29 infants suspected of magnesium depletion retained over 40% of the load. In 16 infants with established magnesium depletion, the most frequent cause was frequent watery stools. One of the patients with serum magnesium levels above the normal range (1.4–1.9 mEq/liter) had a low muscle magnesium level (1.17 mEq/liter; normal = 1.63–2.35) and retained 50% of the test dose. The serum magnesium levels were normal in three who were shown to be magnesium deficient by their retention of more than 70% of the test dose. Not only were the signs of irritability or convulsions improved by the magnesium, but the diarrhea itself showed improvement that seemed related to the magnesium administration. This observation is of particular interest in view of the report by Woodard *et al.* (1972) that an infant with selective malabsorption of magnesium had secondary diarrhea that remitted on repletion of magnesium.

4.6. Protein Calorie Malnutrition (PCM)

The malnutrition seen in infants and young children, kept breast-fed too long to avoid the risk of gastroenteritis encountered on adding food prepared and kept

under unhygienic conditions in undeveloped countries, has been termed kwashiorkor or protein calorie malnutrition (PCM) (Frenk, 1961). Affected children are usually one to four years of age and are generally hospitalized in grave condition after periods of protracted diarrhea, often vomiting, and usually with muscle wasting, dehydration, and trophic disturbances of the skin. There are many variations in therapeutic approaches to the emergency situation, which entail immediate correction of the dehydration by intravenous infusion, followed by skim milk (often protein-fortified), potassium, iron, vitamins, and cottonseed oil (Dean and Skinner, 1957). "Recovery syndromes," with edema, neuroirritability, and (in some geographic areas) cardiovascular abnormalities have been described (Frenk, 1961; Caddell, 1965, 1969a; Wharton *et al.*, 1968), and have been attributed to nutritional imbalances that become manifest, or even provoked by the therapeutic regimen.

Such infants are particularly susceptible to development of hypomagnesemia and tissue depletion of magnesium, particularly when the therapeutic regimen is not only low in magnesium but high in calcium, phosphate, and protein, which lead to new tissue formation and increased magnesium requirements. The first hint that babies (in Uganda) with PCM might have an abnormality in their magnesium metabolism was provided by Schwartz (1956), when she correlated low serum alkaline phosphatase levels of infants with their failure to grow, and showed that their plasma enzyme activity could be increased *in vitro* by addition of magnesium. Standard treatment (in India) lowered alkaline phosphatase activity twofold from levels on admission (Mukherjee and Sarkar, 1958), an observation that further indicates that such a diet might have intensified the magnesium deficiency (Caddell, 1965). Low muscle levels of magnesium in Mexican children with PCM were correlated with blocks in aerobic glycolytic metabolism at Mg-dependent enzymatic steps, e.g., those involving pyruvate and alpha-ketoglutarate metabolism (Metcoff *et al.*, 1960, 1963).

The first demonstration of improvement in clinical response of babies with PCM when magnesium was added to their regimen to correct their hypomagnesemia and low skeletal muscle magnesium levels was in Jamaica (Montgomery, 1960). His magnesium balance studies in such children the following year showed retention of about half the magnesium supplements, even while diarrhea continued. Such additions to the standard regimen resulted in rises in muscle magnesium and potassium, fall in muscle sodium, and improvement in edema (Montgomery, 1961b). His group then showed that the neurologic manifestations of hypomagnesemia and hypocalcemia of severe PCM responded to treatment with magnesium, but not to calcium alone (Back *et al.*, 1962). They later found that, although in some instances the muscle potassium deficit might be even greater than that of magnesium in some PCM children (Alleyne *et al.*, 1970), treatment that corrected the potassium deficit without simultaneously meeting the magnesium needs might have adverse effects (Back *et al.*, 1971/1973). The neurologic signs of 15 of the 20 infants and children with severe gastroenteritis, with and without PCM, developed while they were receiving potassium therapy. They observed that since potassium loads to magnesium-deficient animals precipitate neurologic signs, it would be prudent to correct both deficits clinically. It was noteworthy that seven of the nine infants in their series of 20 who had been severely malnourished did not survive, that their CSF

magnesium levels were subnormal, and that they had cerebral edema on autopsy. Magnesium repletion (2 ml 25% $MgSO_4$), given parenterally, controlled the neuromuscular irritability in 15 of 18 of the infants who had both deficits corrected.

The importance of these findings is indicated by the observations of Wharton *et al.* (1968) that despite lack of agreement as to the best mode of treatment of PCM, all therapeutic regimens include potassium. Although most studies have confirmed the observations of Montgomery (1960, 1961a) and Metcoff *et al.* (1960) that magnesium and potassium losses in muscle of children with PCM usually parallel one another, there has been controversy as to whether magnesium supplements improve the prognosis of children with PCM undergoing treatment. Wharton *et al.* (1968) point out that some of the differences in clinical manifestations of the disease, and in response to therapy, may reflect geographic differences, both in dietary conditions and therapeutic preferences. They point out that in Uganda and Nigeria, cardiovascular complications during nutritional repletion are a considerable risk, while in Jamaica pulmonary edema and hepatic failure are more common; in both those areas and in Central America and India, peripheral edema and neurologic abnormalities are common. It was in Central Eastern Africa that correction of the demonstrated magnesium deficit, precipitated by the standard therapeutic regimen, was shown to reverse the resultant electrocardiographic abnormalities, as well as improve the edema and neurologic status and both morbidity and mortality (Caddell 1965, 1967, 1969a,b; Caddell and Goddard, 1967). All six of the magnesium-supplemented children in the initial study in Uganda (Caddell, 1965) survived; 12 of 21 on the standard regimen died. Extension of her studies in Nigeria (Caddell, 1967, 1969b) showed comparable neurologic and cardiovascular changes among the children on the standard regimen: high-protein milk plus vitamins and minerals (low in magnesium). All 13 Nigerian children with PCM, who had skeletal muscle tissue analyses, showed low levels of magnesium; hypomagnesemia was present in 18 of the 27 children tested (Caddell and Goddard, 1967). The double-blind paired sequential study of 52 severely malnourished Nigerian children, none of whom had shown much improvement on rehydration therapy, was performed to determine the extent to which addition of magnesium to the customary regimen would improve the therapeutic response (Caddell, 1967). The children who received parenteral magnesium could be distinguished from those given equal volumes of isotonic saline by the rise in subnormal temperatures and blood pressures within 24 hours, and general improvement in five days. Fifteen of the 26 magnesium-treated children showed remarkable recoveries. Three died early, and nine developed serious infections, from which only one recovered. In contrast, half of the 16 control children died, three early, two of unknown cause after temporary improvement. Eight died among the 21 who were found to be in the control group when the code had to be broken because of worsening clinical condition; the remaining 13 made remarkable recoveries on substitution of magnesium sulfate for the saline injections. Because magnesium is a hypotensive agent, it had been withheld from the first three children who became hypotensive; they died despite administration of vasopressors and blood transfusions. Later, when it was realized that the magnesium deficiency might be contributory to the hypotension, magnesium therapy was cautiously instituted, sometimes with dramatic improvement. A later report (Caddell, 1969b) considered

the susceptibility of PCM children on standard therapy to congestive heart failure, when given blood transfusion, and their subsequent high incidence of digitalis toxicity. During a 2- to 12-month follow-up period of 32 children who survived their severe PCM, and who had received parenteral magnesium, Caddell (1969a) contrasted the sustained rapid improvement in her series of patients, with the persistent abnormalities and stunting for prolonged periods of time, and high mortality rates among the PCM children who had not received magnesium supplements reported by others.

Evidence of magnesium depletion in children with PCM, comparable to that seen in Uganda and Nigeria, has been reported from Senegal (Ingenbleek and Giono, 1971/1973). Hypomagnesemia (mean = 1.1 mEq/liter) was noted on admission in the 11 babies whose magnesium and nitrogen balances were studied for 23–30 days, while they were on oral magnesium supplements (240 mg Mg/48 hours). Cumulative magnesium retention reached about 2 g. This group of investigators had found, earlier, that the signs of neuromuscular irritability had been intensified after the first week or two of protein repletion in a small percentage of severely ill babies, during which time their initially strongly positive magnesium balance dropped sharply. When the diet was gradually improved and supplemented with magnesium, the magnesium balances steadily became more positive and the "recovery tetany syndrome" did not develop. Unlike the repletion of potassium, which had been accomplished by 10 days of oral potassium chloride, independent of the rate of nitrogen retention (Ingenbleek *et al.*, 1968), the magnesium repletion seemed linked with that of nitrogen retention.

The dietary staple (maize) among the Bantu in South Africa being richer in magnesium than in the main dietary constituent in Central Africa, cassava (Rosen, 1971), it is not surprising that the magnesium deficiency of children with PCM in that area has been less severe, and that their responses to magnesium supplementation less striking. Linder *et al.* (1963) found that Bantu infants with PCM fed skim milk alone, supplemented by infusions to combat dehydration when necessary, produced positive magnesium balances. However, five of the children, who were also given 130 mg of magnesium daily retained twice as much magnesium as did the patients without the supplement. Those given magnesium also retained more calcium than did those on milk alone. The mean serum magnesium levels of the babies given magnesium supplements reached almost normal levels within the first nine days of treatment; the mean levels of those receiving no supplement remained at 1.2 mEq during the same period. From days 10–22, the mean serum magnesium levels of the supplemented babies reached 1.6 mEq/liter; that of those without supplements rose to 1.4 mEq/liter. Thereafter, there was little difference in serum levels in the two groups. Pretorius *et al.* (1963), also in South Africa, found that babies with PCM did not have serum and erythrocyte levels of magnesium as low as did Jamaican babies with PCM (Montgomery, 1960, 1961a). Nonetheless, they retained up to 60% of parenterally administered magnesium, very small amounts of which appeared in the urine. They had malabsorption of magnesium that persisted, even after diarrhea had abated. Rosen *et al.* (1970) did not confirm Caddell's (1967) findings of improved therapeutic response in their South African study of 100 consecutive children with PCM, 50 assigned to the standard regimen and 50 to the same

basic regimen plus magnesium supplementation. The mortality rates in both groups were 21% (most early after admission) and the rates of recovery were the same. The serum magnesium levels were slightly lower than normal in the children with PCM, but the differences in incidence of low and high in the groups on standard and magnesium-supplemented regimens did not differ substantially. This group (Rosen *et al.*, 1970) did not have to break the code before completion of the study because of worsening clinical condition, as did Caddell (1967). Unlike the children in Nigeria and Uganda, electrocardiographic changes that improved when magnesium was added were not part of the recovery syndrome on the standard regimen in South Africa.

Studies from India have confirmed the magnesium depletion of young children with PCM (Agarwal *et al.*, 1967; Bajpai *et al.*, 1970; Chhapparwal *et al.*, 1971a; S. Mehta *et al.*, 1972). Although low blood magnesium levels have been reported frequently, serum and erythrocyte levels did not always reflect the status of magnesium in the body. Bajpai *et al.* (1970) compared the levels of magnesium in plasma, erythrocytes, and skeletal muscle in children with PCM and in a group of children, some of whom were convulsing from "minor ailments" (Table 4-5). Since magnesium deficiency can be implicated in pediatric convulsive states, it is uncertain that the range for the controls reflects optimal magnesium levels. The magnesium blood levels of the PCM children who had diarrhea were lower than in those without diarrhea, an expected finding in view of the magnesium deficiency caused by inflammatory or metabolic intestinal disease. Almost a third of the children with PCM had plasma magnesium levels below 1.40 mEq/liter; half had erythrocyte magnesium levels below 3.50 mEq/liter packed cells. The muscle magnesium levels were 30% lower in the PCM children than in the three controls whose muscles were biopsied.

TABLE 4-5. Magnesium Levels in Plasma, Erythrocytes, and Skeletal Muscle of Normal and Malnourished Children [a]

	Protein calorie malnutrition [b]	Controls [c,d]
Plasma Mg (mEq/liter)	On admission Total: 1.17–2.05 (Mean: 1.60) Without diarrhea: 6 (Mean: 1.86) With diarrhea: 18 (Mean: 1.52)	1.63–2.25 (Mean: 1.76)
Erythrocyte Mg (mEq/liter)	2.21–4.90 (Mean: 3.56) Without diarrhea: 6 (Mean: 3.74) With diarrhea: 18 (Mean: 3.51)	3.20–5.30 (Mean: 4.76)
Muscle Mg (mEq/kg wet weight)	17 cases (Mean: 11.38)	3 cases: 17.98 17.78 18.00

[a] Adapted from Bajpai *et al.* (1970).
[b] Average age: 32 months. Total: 24 patients.
[c] Age range: 12–48 months. Total: 21 patients.
[d] Normal or convulsing from minor ailments.

Comparison of magnesium levels of eight children given parenteral magnesium (1–1.5 ml, 50% $MgSO_4$ for three days and then 1 ml on alternate days) for 18–20 days (randomly allocated) and those not so supplemented showed that the magnesium-supplemented children exhibited significantly increased erythrocyte magnesium levels, as compared with those getting standard therapy. Only slight increases in plasma and muscle magnesium levels were noted in those getting magnesium; three of four patients (not on magnesium) who were again biopsied showed decreased muscle magnesium levels. The minimal increases in muscle magnesium, even in those being supplemented, suggested to the investigators that the demand outstripped the supply.

Caddell's investigations of PCM children in Thailand provide evidence of the difficulty in selecting laboratory tests that reliably indicate magnesium depletion in such children. In the first of these studies (Caddell and Olson, 1973), 44% of the 30 children had serum magnesium levels just below the lower limit of normal at the time of admission, but 93% had significantly low urinary Mg outputs; muscle magnesium levels were almost half the published normal value. After 16 hours of parenteral fluids that had no magnesium, 56% of the plasma Mg levels had decreased. The lowest plasma magnesium values developed between days 5 and 14, when plasma albumin and other electrolytes were attaining normal levels. Anorexia persisted longer in the children with plasma levels of magnesium below 1.2 mEq/liter than in those with higher levels. Pitting edema, T-wave abnormalities, and neurologic signs and symptoms correlated with levels below 1.0 mEq/liter during the early treatment period. Continued diarrhea, prolonged intravenous therapy, and anorexia were contributing factors to the drop of plasma magnesium levels to 1.0 mEq/liter in 17 children who were being treated with magnesium. Normal plasma magnesium levels were attained in all but one child by three weeks, but almost one-third still had low urine magnesium values. There was little difference between 24-hour urinary outputs of magnesium in those receiving and those not receiving magnesium supplements; both groups had hypomagnesiuria. Muscle magnesium levels increased slowly and were still low at 11 weeks. In the second study of Thai children with PCM (Caddell *et al.*, 1973), the parenteral magnesium load test was utilized to provide a better clue to the magnesium status of these malnourished children, before and in the course of nutritional repair. Low preload urinary magnesium excretion was not found a helpful guide in this series of children, who had relatively mild hypomagnesemia. Seven of 25 children, who excreted less than 1 mEq/liter/24 hours, retained a mean of only 23% of the magnesium load. There was no significant correlation between magnesium retention and edema; children with antecedent diarrhea retained much of the magnesium load.

Aguilar (1971/1973) and Cheek *et al.* (1970) found that Peruvian PCM children retained both magnesium and potassium, in proportion to that of nitrogen, but that the minerals were more quickly retained than was the nitrogen. Low muscle magnesium levels were found in the PCM children before and four to nine months after treatment (Cheek *et al.*, 1970). In a detailed metabolic study from Guatemala (Nichols *et al.*, 1978), it was found that increasing the daily oral magnesium supplement to 0.42 mEq/kg/day, from the amount (0.12 mEq/kg/day) that had been found insufficient for adequate retention (Nichols *et al.*, 1974), resulted in five to six times

greater magnesium retention and markedly increased muscle magnesium levels. Provision of 2.7 mEq/kg/day (from oral and parenteral supplements of magnesium) was not essential for clinical recovery from the edematous form of PCM, but their response was more rapid than was that of those on the lower supplements. Their muscle potassium levels returned to normal earlier, and on a constant intake their potassium retention was increased threefold during the magnesium supplementation. Considering the insensible losses of magnesium (i.e., from skin), the amount required for restoration of deficit, and that needed for formation of new tissue, Nichols *et al.* (1978) estimate that the oral magnesium requirement during initial stages of treatment of PCM may be as high as 2.7 mEq/kg/day (32 mg/kg/day). When diarrhea interferes with absorption, combination of parenterally administered and oral magnesium is necessary.

Aguilar (1971–1973) made an interesting observation on the failure of the kidneys of the infants with PCM to retain magnesium when their Mg supplements were discontinued. Whether this implies tubular damage like that found in magnesium-deficient rats (J. Oliver *et al.*, 1966) and in an infant with primary malabsorption of magnesium (Vainsel *et al.*, 1970) remains to be determined. Renal damage in the area where magnesium is reabsorbed may intensify magnesium deficiency or make repletion difficult (Seelig *et al.*, 1979). It has been shown, however, that children with PCM have subnormal renal function (Nichols *et al.*, 1974).

4.7. Sudden Death in Infancy: Possible Role of Magnesium Deficiency

4.7.1. Sudden Infant Death Syndrome (SIDS)

There are few more tragic events than the sudden death of an infant who seemed healthy, was growing well, and had few signs of anything wrong more serious than a slight respiratory infection, irritability, or feeding difficulties a day or two before being found dead in his crib. Research into the literature has disclosed such events throughout history; epidemiologic studies and reviews show that they are most common in the winter to spring months and most often occur in infants of young and multiparous mothers (Valdes-Dapena, 1967; Geertinger, 1967; Froggatt *et al.*, 1968; Marshall, 1972). The incidence is about 1 in 400–500 live births; over 20,000 are estimated to occur annually in the United States (Froggatt *et al.*, 1968; Valdes-Dapena, 1973). The etiology of such deaths remains undefined. Asphyxiation and parental neglect used to be blamed. The major theories now include (1) viral infection and immunologic abnormalities or histamine shock (Froggatt *et al.*, 1968; P. Gardner, 1972; Caddell, 1972; Ogra *et al.*, 1975; Caddell, 1975/1977); (2) disorders of the autonomic system (Salk *et al.*, 1974; Naeye, 1976; Naeye *et al.*, 1976a) that can lead to periods of apnea, such as are frequently implicated in SIDS (Steinschneider, 1972; Naeye, 1973; Guilleminault *et al.*, 1975); and (3) abnormalities in cardiac conduction tissue and electrical instability of the heart (T. James, 1968; J. Ferris, 1972, 1973). Swift and Emery (1972) question the histamine theory,

since they found no degranulation of pulmonary mast cells in SIDS victims. Also controversial is the theory that such infants have abnormal conduction tissue (Valdes-Dapena *et al.*, 1973; Lie *et al.*, 1976; T. James, 1976). A fortuitous study of cardiac lability in a group of healthy infants, one of whom later died suddenly, showed that the prestimulus variability in heart rate of the SIDS infant was significantly deviant from the other 23 infants subjected to auditory stimuli; his peak accelerated rate was higher (Salk *et al.*, 1974). Increased muscle mass of the pulmonary arteries have been detected in SIDS victims, and considered a possible consequence of chronic alveolar hypoxia that might reflect the periods of sleep apnea (Naeye, 1973; Naeye *et al.*, 1976a,b).

4.7.1.1. Acute Magnesium Deficiency, Histamine Release, and Hypoxia in SIDS

The possibility that magnesium deficiency of growth might be a major factor in the etiology of SIDS has been postulated by Caddell (1972). She points out that premature and low-birth-weight infants with poor magnesium stores and low birth weights are most vulnerable to sudden unexpected death. She reviewed the evidence that this condition used to occur in breast-fed infants of destitute multiparous mothers, but that it is now chiefly a problem of infants (often overweight) fed artificial formulas and cereal foods that provide high contents of calcium, phosphorus, and protein. The development of hypomagnesemia in formula-fed infants, often in association with hypocalcemia despite the higher content of calcium in cows' than in human milk has been discussed earlier. Formula-fed infants commonly grow faster than do breast-fed infants, and have lower plasma magnesium, as well as calcium levels, and higher phosphorus levels. Thus, they may well fit into Caddell's (1972) "magnesium deprivation syndrome of growth," particularly when they are born to mothers whose magnesium status may be suboptimal or poor, and thus might have insufficient magnesium stores at birth. Maternal hypomagnesemia has been demonstrated in precisely those women whose infants are at greatest risk of SIDS: women with preeclampsia or eclampsia, who are themselves immature and whose diets do not meet their own growth requirements of magnesium, or who are of high parity, particularly when the pregnancies have been at frequent intervals. Infants born to such mothers, especially if the birth is multiple, probably have low magnesium stores. Support for this premise derives from the observation that the young of magnesium-deficient pregnant animals are more magnesium deficient than are the mothers (Cohlan *et al.*, 1970; Dancis *et al.*, 1971; Wang *et al.*, 1971) holds true for human infants. Caddell (1972) has pointed out that premature infants, whose magnesium stores are proportionally less than are those of a full-term infant (Widdowson, 1965), and who have high growth rates, might reach critically low levels of magnesium that might trigger the SIDS. She compares their premonitory and terminal signs to those of acute magnesium deficiency in immature animals and to those in infants recovering from severe gastroenteritis of protein calorie malnutrition, among whom sudden death has been reported during the recovery period, at which time new tissue formation increases magnesium requirements.

One may question whether the "sniffling" or signs of a minor respiratory ailment, which is commonly reported as a premonitory sign of SIDS, is the human counterpart of the reddened, inflamed snout and ears of magnesium-deficient animals. Such reactions might reflect histamine release, and magnesium deficiency has indeed been shown to increase degranulation of mast cells and to increase histamine blood and urinary levels (Hungerford and Karson, 1960; Bois, 1963; Bois *et al.*, 1963; Bois and Jasmin, 1971/1973). The similarity of some of the SIDS necropsy findings to those of anaphylactic shock, with hemorrhagic and edematous pulmonary changes, supports Caddell's hypothesis that the sudden death might be mediated by release of histamine.

Although neuroirritability is common a day or two before the sudden death (Caddell, 1972), the typical picture of acute experimental and clinical magnesium deficiency, seizures and electrocardiographic changes, is usually not characteristic of the SIDS. Tonic–clonic seizures have been reported in SIDS, but a retrospective survey of the temperament of victims of SIDS provides evidence of less intense reactions to environmental stimuli than had been exhibited by normal siblings (Naeye *et al.*, 1976a). They were less active, more often breathless and fatigued, and had more shrill cries. A prospective study found additional evidence of central nervous system dysfunction, including neonatal abnormalities in respiration, labile temperature regulation, and weak suck reflexes. Despite the commonly held assumption that the SIDS strikes infants who were completely well before the catastrophe, Naeye *et al.* (1976a), obtained evidence that only a third of the SIDS victims were completely free of illness or unexplained crying.

4.7.1.2. Subacute Magnesium Deficiency and Cardiac Lesions in SIDS

Just as magnesium deficiency can be implicated in histamine release (as a contributory factor to the SIDS), perhaps a less acute magnesium deficiency might also be involved in cardiac changes, described in the conduction tissue of infants with the SIDS, and that can cause sudden death as a result of acute arrhythmias. Magnesium deficiency and agents that increase myocardial magnesium loss have been utilized in many experimental models of myocardial necrosis (Reviews: Lehr, 1969; Seelig, 1972; Seelig and Heggtveit, 1974). As in those models, infantile coronary arteriosclerosis generally involves the small intramyocardial arteries, with perivascular foci of infiltration, necrosis, and fibrosis. If the areas of necrosis involve the conduction tissue, even small foci can induce arrhythmias and sudden death (T. James, 1967). The high lability of magnesium in the interventricular septum and left ventricle (p.187) suggest that these areas are at particular risk in infants with suboptimal magnesium. It is not yet clear whether small coronary lesions contribute to damage to the conduction system of the heart in the SIDS (T. James, 1968; Ferris, 1972, 1973; Valdes-Dapena *et al.*, 1973; T. James, 1976). W. Anderson *et al.* (1970) found focal intimal and medial hyperplasia of the A-V node artery with luminal narrowing in 35% of the SIDS cases and in 10% of 22 control infants of the same age (between one and two months). However, resorptive and degenerative changes involving portions of the A-V node and bundle of His was present in all SIDS and control cases. They speculate that dysfunction associated with these processes

might be contributory to the SIDS. Ferris (1973) has commented that the changes in the conductive tissue of the heart of infants with the SIDS is akin to the form of ischemic fibrosis that is seen with adult coronary arterial disease. Valdes-Dapena *et al.* (1973) observed petechiae in the conduction system of 26% of SIDS infants and 20% of control infants in their group of 47 who had died in the first year of life, an insignificant difference. They noted that 50% of the 31 SIDS infants had minute myocardial hemorrhages and that 37% of the 16 controls had similar hemorrhages in the myocardium near the conduction system. However, they disagreed that there were connective tissue changes near the conducting system that might explain the sudden deaths. It should be noted that the myocardial hemorrhages described in both groups seem to indicate some abnormal process; that they occurred in both groups might reflect a common underlying abnormality. Among the control infants were 6 with pulmonary disease (infection or hyaline membrane), 1 with methemoglobinemia, 1 who was premature, and 2 with diseases causing severe diarrhea; all are conditions that might well have caused loss of myocardial magnesium.

4.7.1.3. SIDS and Hypoparathyroidism

Another condition that has been directly associated with the SIDS is infantile hypoparathyroidism, a condition associated with maternal hyperparathyroidism and with neonatal hypomagnesemia, hypocalcemia, and hyperphosphatemia. The study of 82 autopsied cases of SID (Geertinger, 1967) showed that in a third of the infants, no parathyroid gland could be found. In the others there were abnormalities in parathyroid localization and morphology, often with fusion with thymic tissue. The author speculated that maternal hyperparathyroidism might result in congenital anomalies of the parathyroids. Thus, the experimental model that might be most revelant to the cardiac damage of infants in the first few months of life, and consequently to the SIDS and to other sudden deaths and cardiac lesions during infancy, is the parathyroidectomized, phosphate-loaded rat that develops lesions of the small coronary arteries and of the perivascular myocardium (Lehr, 1959, 1965). Neonatal infants are commonly hypoparathyroid, and those fed cows' milk formulas are also hyperphosphatemic. Those born with poor magnesium stores are particularly vulnerable to lesions of the small coronary arteries, such as have been produced in "pure" magnesium-deficient animals, and intensified by phosphate loads (Review: Seelig and Haddy, 1976/80).

Hyperparathyroidism in the mother, which predisposes to infantile hypoparathyroidism, might be the result of maternal hypomagnesemia. Resultant mobilization of maternal calcium, and its transfer to the fetus, militates against fetal hyperparathyroidism, and has in fact been implicated as the cause of infantile hypoparathyroidism, which is often associated with hypomagnesemic hypocalcemia. That infantile hypomagnesemia can be associated with congenital absence of the parathyroids and thymic abnormalities [such as Geertinger (1967) showed in the SIDS], has been reported by Taitz *et al.* (1966) in an infant with neonatal tetany associated with persistently low serum magnesium levels. Niklasson (1970) reported two sisters with similar manifestations and hypomagnesemic hypocalcemia in a family with a high incidence of hypoparathyroidism. Eight members of

the family had died during infancy, one at four weeks of "sudden unexplained death" and four with convulsions at under six months.

The role of hypomagnesemia in refractory hypocalcemia of infancy suggests that, in addition to the association of hypocalcemia with recurrent apnea of premature infants (Gershanik *et al.*, 1972), the magnesium status should also be ascertained. The investigators (Gershanik *et al.*, 1972) found no difference in the overall mean magnesium levels between the infants who did or did not suffer attacks of apnea. In view of the egress of magnesium from cells, however, in response to hypoxia the normal serum magnesium levels in infants with recurrent apnea cannot be accepted as proof that magnesium deficiency was not present. Measurement of retention of a parenteral magnesium load would provide a more reliable index of the infants' magnesium status (Harris and Wilkinson, 1971; Caddell, 1975).

Far from all infants who die suddenly are autopsied; many are classified as SIDS on the basis of the clinical history, no clear medical explanation for the death having been noted. However, only a third of the SIDS infants had had no premonitory signs (Naeye *et al.*, 1976a). Intensive interviews with their parents disclosed that most had tended to be more subject to breathlessness and exhaustion during feeding than were their siblings, and to have less reactivity to environmental stimuli. These manifestations are not unlike those reported for infants found at autopsy to have cardiovascular lesions, such as coronary artery disease (with or without myocardial infarcts), endocardial fibroelastosis, or both, and who—although they often died suddenly—are thus not included in the SIDS category. (Sudden death was reported in about one-fourth of the infants reported in Appendix Tables A-5A and A-6A.) Their prodromal symptoms, however, resemble those described in SIDS. Sudden onset of respiratory distress in previously well-nourished, thriving infants was the presenting finding in many of the infants found to have coronary disease, endocardial fibroelastosis, or focal myocardial lesions at autopsy. Cyanosis and intermittent episodes of pallor and cold sweats were common. Most died within a few hours to a few days after the onset of the sudden illness. Many of the infants also presented with feeding difficulties and vomiting, often of sudden onset. ECG tracings typical of ischemic heart disease were sometimes obtained.

4.7.1.4. Epidemiologic Factors in SIDS

Since magnesium deficiency has been implicated in sudden death from ischemic heart disease in adults, the incidence of which is much higher in soft-water areas with low magnesium content than in hard-water areas (T. Anderson *et al.*, 1975, 1979), and since a highly significant negative correlation has been found between infant mortality and water hardness (M. Crawford *et al.*, 1968, 1972), it may be that magnesium deficiency in soft-water areas is contributory to the SIDS and to diagnosed infantile cardiovascular disease. This group noted that the correlation was much higher in the 1968 and 1972 studies than it had been in a 1951 analysis, and proposed that water minerals might play an important role in infant mortality that became manifest as "social" factors became less important. In 1972, M. Crawford *et al.* selected older mothers and those of high parity as being at high risk for both stillbirths and infant deaths, and found that the highest incidence of

stillbirths and postneonatal infant deaths occurred in women of parity 3+ and in areas with the softest water. They speculated that it was the low calcium level in the soft water that was the risk factor. They did not include magnesium determinations in the 1972 study, but in the 1968 study gave data showing that the magnesium level in soft-water communities was about a quarter that of the hard-water communities.

Studies from Finland provide further data that suggest that it might be the amount of magnesium consumed that influences susceptibility to sudden death from ischemic heart disease, not only in adults but in infants. Karppanen and Neuvonen (1973) pointed out the clear-cut regional distribution of ischemic heart disease in Finland, being twice as high in eastern as in southwestern Finland. It is thus of interest that the magnesium content in the east Finland soil is one-third that of southwest Finland. A study of the thickness of the inner layers of the coronary arteries of infants showed that infants from families from the eastern parts of Finland had significantly thicker coronary arteries than did those from the southwest, a finding correlated with a higher rate of adult ischemic heart disease in the eastern part of the country than in the southwest (Pesonen *et al.*, 1975). There has also been a report from Finland of infant death in the first three children born to consanguinous parents (Meurman *et al.*, 1965). The first died one hour after birth, the victim of birth asphyxia. The second thrived until six weeks, at which time she suddenly refused her feedings, had screaming attacks, and died before she could be hospitalized. Autopsies were not performed. The third infant developed identical symptoms to that of the second, at six weeks of age, and died suddenly at night. She had the typical coronary lesions of infantile arteriosclerosis. This family lived in Kuopio, in the northeastern part of Finland. Possibly contributory might be frequency of pregnancies in the presence of suboptimal magnesium intake. However, at the time of the publication, the fourth and fifth children were well at two years and at four months, respectively. Follow-ups of these infants are not available.

There is an overlap in the months during which the greatest number of infants die with the SIDS and in which most cases of infantile tetany have been reported. A survey of the world literature showed that there were twice as many cases of SIDS during the colder months of the year (Valdes-Dapena, 1967), a finding confirmed by an epidemiologic survey in Ireland indicating that the peak incidence occurred between February and March (Marshall, 1972). It is provocative, thus, that the serum calcium levels were low during gestation in the winter months (Mull and Bill, 1934) despite their hyperparathyroidism (Bodansky and Duff, 1939), and that neonatal tetany, a condition that is correlated with transient hypoparathyroidism and hypomagnesemic hypocalcemia, has also been shown to be most frequent in the cold months (Saville and Kretchmer, 1960). The possibility that hypoparathyroidism might be implicated in the SIDS (Geertinger, 1967) has been considered, as has the possible role of parathyroid deficiency in damage to small coronary arteries and in perivascular myocardial necrosis. Ludwig (1962), who reviewed the status of infants born of hyperparathyroid mothers, found of the 40 infants reported (presumably hypoparathyroid, at least at birth) there were 9 who were stillborn or aborted, 5 who died shortly after birth, and 5 who developed neonatal or later tetany. Five of the infants were premature.

4.7.1.5. Need for Further Study

Magnesium determinations are almost never reported in mothers or siblings of infants who died of the SIDS or of proved cardiac failure or arrhythmias, or in infants with congenital cardiovascular disease. Convulsions, the condition that most often leads to such tests, are rarely part of the prodromata of infants with these disorders. Although low-birth-weight infants, multiple births, those born to diabetic mothers or to multiparous mothers have been evaluated for serum magnesium levels, there is a paucity of follow-up data as to the incidence of the SIDS or cardiovascular disease in such infants. Because hypoxia causes egress of magnesium from the tissues, serum magnesium levels might provide unreliable assurance of normal magnesium body levels in infants with cardiac failure. Determination of the magnesium status by ascertaining the percentage retention of a loading dose is of value if the renal function is normal. Improved techniques are necessary for evaluation of cellular levels of functional magnesium. Caddell and her colleagues are addressing themselves to a systematic survey of the SIDS problem, attempting to determine whether maternal magnesium deficiency, as determined by retention of load-test, is participatory (Caddell, 1975, 1977; Caddell *et al.*, 1975). Similar surveys of mothers and siblings of infants who died of coronary arteriosclerosis and other cardiac lesions, as well as of babies with congenital cardiovascular disease, is also indicated.

II

MAGNESIUM DEFICIENCY IN THE PATHOGENESIS OF CARDIOVASCULAR DISEASES

5
Failure to Reduce Incidence of Ischemic Heart Disease by Lowering Blood Lipids

Cardiovascular diseases continue to represent the major cause of morbidity and mortality in the developed countries, especially in young men, despite the considerable efforts and funds expended in the effort to explain and reverse the atherosclerotic process by studying and modifying fat intakes. Ischemic heart disease (IHD) is responsible for over 54% of all deaths in the United States (U.S. Dept. HEW, 1970); it is the major cause of death in most affluent communities (Editorial, *Brit Med J,* 1972). That the problem has increased during this century, particularly in young and middle-aged men, is indicated by two types of studies: (1) retrospective analyses of large numbers of necropsies (over 6000 each) in a large city hospital (Saphir *et al.,* 1956) and from the Armed Forces Institute of Pathology (Pettyjohn and McMeekin, 1975); and (2) examination of the hearts of military men coming to autopsy in World War II (Yater *et al.,* 1948, 1951; Moritz and Zamcheck, 1947), the Korean War (Enos *et al.,* 1955), and the Vietnamese War (Macomber, 1971; McNamara *et al.,* 1971; Wroblewski, 1971), and of victims of aircraft fatalities (Glantz and Stembridge, 1959). The study at Michael Reese Hospital in Chicago (Saphir *et al.,* 1956) showed that there was an increase in frequency of coronary artery disease in subjects under 50 from 5.9% in 1920–1939, to 14.1% in 1940–1949, to 25.5% in 1950–1953. This did not take into account the almost twofold greater frequency of IHD in men than women. Pettyjohn and McMeekin (1975) found that 13% (816) of 6500 autopsied cases from aircraft accidents had been diagnosed as having had preexisting heart disease. Of those 816 cases (592 military and 135 civilian), 89.1% had coronary artery disease. Among the 380 men, 20–34 years of age, an upward trend was noted in the incidence of moderate to severe coronary artery disease from 1960–1964 to 1965–1969. (Too few autopsies were available for the 1970–1974 study for valid comparison.) In the studies of soldiers in the last three wars, startlingly high numbers of young men were found to have IHD. Yater *et al.*

(1948) studied heart tissue from 866 American World War II soldiers, between 18 and 39 years of age, who developed IHD; 450 of these were examined at autopsy. From the incidence among soldiers, they estimated that the IHD death rate, per 100,000 men was less than 0.1 at 18–19, 1.0 at age 25–29, 3.4 at age 30–34, and 12.7 at age 35–39. Moritz and Zamcheck (1946) reported 115 sudden deaths from IHD in additional young soldiers. In the study of 300 American soldiers killed in Korea (Enos *et al.*, 1955), 77% had histologic evidence of coronary disease; the average age was 22.1 years. The 1959 study of material from Air Force fatalities (Glantz and Stembridge, 1959) showed that 70% of 222 men of 20–44 had coronary disease, the highest incidence being in men 30–34, 35–39, and 40–44 years of age who had moderate to advanced arteriosclerosis in 32%, 26%, and 50%, respectively. There was a difference of opinion as to whether there was, indeed, a lower incidence of coronary artery disease among American soldiers killed in Vietnam (McNamara *et al.*, 1971; Macomber, 1971; Wroblewski, 1971). Pettyjohn and McMeekin (1975) analyzed the factors contributing to the seeming decline in IHD incidence (McNamara *et al.*, 1971) and attributed this finding to a difference in parameters used in classification of disease. The relative increase in mortality rates from IHD in the younger age groups has been confirmed by the international studies (International Workshop in Cardiovascular Disease, 1959–1969; Fejfar, 1974) even from groups employing measures to lower blood cholesterol levels (Fejfar, 1974).

As a result of the failure to prove that the incidence of deaths from IHD can be lowered by changing the fat intake of patients with the disease (Editorial, *Brit Med J*, 1972, 1976b; Stolley, 1972; Fredrickson, 1972; Fejfar, 1974), there has been revival of interest in the likelihood that adult cardiovascular disease has its roots in infancy, and that that is the time to change the fat in the diet (U.S. Dept. HEW, 1970; Glueck and Tsang, 1972; Glueck *et al.*, 1972; 1974a). This approach is based on three findings: (1) the detection of fatty intimal streaks in arteries of infants and children (Duff and McMillan, 1951; R. Holman *et al.*, 1958; R. Holman, 1961; Reisman, 1965; Strong and McGill, 1969); (2) the correlation of hyperlipidemia with increased risk of early arteriosclerosis (Gofman *et al.*, 1950; Keys, 1956; Gertler *et al.*, 1959; Berenson *et al.*, 1974); and (3) the evidence that children of victims of early heart attacks often have hyperlipidemia (Tamir *et al.*, 1972; Glueck *et al.*, 1974b; H. Chase *et al.*, 1974). Furthermore, large-scale screening programs have shown that three-year-old children already have cholesterol levels similar to those of young adults (Berenson *et al.*, 1974). At present, it is considered feasible only to screen children with parenteral histories of early IHD (H. Chase *et al.*, 1974; North, 1975; Laird, 1975). A general change of diet, so as to institute hypolipidemic regimens has been suggested (U.S. Dept. HEW, 1970). Altering the fat content of infants' diets substantially has been criticized because not all of the etiologic factors in arteriosclerosis are known, and because the results of the field trials have not yet proven that substituting unsaturated for saturated fatty acids will prevent coronary heart disease, even though they have lowered blood lipids (Stolley, 1972; Fredrickson, 1972; C. Lowe, 1972; Levy *et al.*, 1974; North, 1975; Laird, 1975). Furthermore, the potential risks of such diets remain to be ascertained (Foman, 1974; Schubert, 1973; Laird, 1975; Glueck *et al.*, 1975/1977).

Thus, the need for searching out coronary-risk indicators persists (Blackburn,

1974). Changes in the musculoelastic layer of coronary arteries of infants and children are again being considered as the possible initial lesions in the atherosclerotic process (Neufeld, 1974; Danilevicus, 1974). The first visible changes in the internal elastic membrane, its splitting or fragmentation, are seen within a few days after birth (or in some cases in stillborn infants) and become more prominent in the first month of life (Bertelsen and Jensen, 1960; Bertelsen, 1961; Neufeld and Vlodaver, 1968, 1971, 1974; Neufeld, 1974). These are changes that have long been proposed as the first departure from normal, and that should be considered a manifestation of early arteriosclerosis and the basis for development of atherosclerotic lesions (Merkel, 1903; Jores, 1924; Minkowski, 1947; Fangman and Hellwig, 1947; Levene, 1956; Moon, 1957; Pizzagalli and Bertana, 1959; Bertelsen, 1961; Kaunitz, 1961; Gillot, 1962).

Many factors contribute to the metabolic abnormalities that lead to different blood, arterial, and cardiac biochemical, functional, and histological changes that represent aspects of the complex of cardiovascular diseases. Vitamins B_6 and E have been suggested as protective against arteriosclerosis. Vitamin B_6 has been suggested by Rinehart and Greenberg (1949, 1951, 1956), Moon and Rinehart (1952), Moon (1957, 1959), Boxer *et al.* (1957), Hass (1961), and Levene and Murray (1977). Vitamin E has been suggested in peripheral disease, e.g., intermittent claudication, by Livingstone and Jones (1958), Haeger (1968, 1973), Larsson and Haeger (1968), and Williams *et al.* (1971); in thrombotic disease by Zierler *et al.* (1948), Ochsner (1951), Suffel (1956), and Kawahara (1959); and in the controversial use in heart disease by Vogelsang *et al.* (1947; publications of the Shute Institute). Pyridoxine/blood– and tissue–lipid interrelationships have long been known (Birch, 1938; Medes and Keller, 1948; Schroeder, 1955; Shah *et al.*, 1960; G. Emerson *et al.*, 1960; Lupien, 1968), and combinations of the vitamins, sometimes with A (Hammerl and Pichler, 1960) proposed. Vitamin C has been shown to lower plasma cholesterol levels, and by inference atherosclerosis (Spittle, 1970, 1971; Anderson *et al.*, 1972). However, hypercholesterolemia has been produced in rats by supplements of vitamin C equivalent to excesses of less than one gram over that in the diet, an effect attributed to ascorbic acid induced production of high zinc/copper ratios (Klevay, 1977). Thiamine deficiency has been shown to increase the hepatic synthesis of lipids by rats; hypertriglyceridemia of magnesium deficiency develops in the presence of adequate or excess thiamine, but not in double deficiency (Itokawa *et al.*, 1973). Excess vitamin D increases arteriosclerosis both in experimental animals and in man—infants, children, and adults. In his epidemiologic correlation of only slightly higher than recommended intakes of vitamin D with increased incidence of myocardial infarction, Linden (1974b) suggested that the hypocholesterolemic effect of vitamin A might protect against the hypercholesterolemic action of vitamin D. Additional studies confirm that experimental A deficiency increases both atherosclerosis and cholesterol blood levels (Bayer *et al.*, 1972; Bonner *et al.*, 1973). In 1962, I. Clark and Bassett showed that vitamin A decreased other manifestations of vitamin D toxicity: osteolysis and renal and arterial calcinosis. As early as 1939, Reed *et al.* reviewed the data on vitamin D toxicity and reported that in the absence of vitamin A, the lesions of hypervitaminosis were worse.

Several of these vitamins are of interest in this presentation because they affect

magnesium metabolism, influence the response to magnesium, or affect magnesium requirements. For example, vitamin B_6 deficiency causes arterial lesions (Rinehart and Greenberg, 1949, 1951) very much like those of magnesium deficiency (Hass, 1961), and gestational B_6 deficiency has been blamed for the elastica damage of neonatal arteriosclerosis (Levene and Murray, 1977), in which magnesium deficiency is implicated in this book. Interrelationships of magnesium and pyridoxine metabolism have been reviewed by Durlach (1969b). The response of B_1-deficient animals (Zieve *et al.*, 1968a,b; Zieve, 1969) and man (Zieve, 1975) is magnesium dependent. The cardiovascular lesions of vitamin D excess might be partially implemented by magnesium loss. Vitamin D increases magnesium loss by increasing its renal excretion relative to its absorption (Hanna, 1961b; Richardson and Welt, 1965; Wallach *et al.*, 1966). Infants and children with hypervitaminosis D, who develop hypercalcemia, the supravalvular aortic stenosis syndrome (SASS), and other stenotic and hypoplastic lesions of the greater arteries, also develop peripheral arterial lesions (including atheromata and calcinosis), hypercholesterolemia, and hypertension. Since vitamin D excess causes calcium retention as well as magnesium loss and high calcium/magnesium plasma ratios have produced increased arterial resistance (Review: Haddy and Seelig, 1976/1980, and *infra vide*), the combination of low magnesium stores at birth and high vitamin D and calcium intakes in infancy can be responsible for several metabolic and histologic aberrations leading to cardiovascular diseases.

The similarity of the arterial lesions, and of the microfocal myocardial necrosis seen in the infants, to those produced experimentally by essentially "pure" magnesium deficiency (Seelig and Haddy, 1976/1980) has suggested magnesium deficiency during gestation and infancy. Furthermore, magnesium deficiency, even in the absence of hypervitaminosis D, has been shown to cause abnormal changes in blood lipids (Review: Seelig and Vitale, 1971/1973).

Epidemiologic data point both toward magnesium as a protective factor against sudden death from ischemic heart disease and toward even slight to moderate excesses of vitamin D as a risk factor in hyperlipidemia and myocardial infarction (Review: Linden, 1975/1977). Experimental data demonstrate that magnesium is protective against several models of myocardial disease, including those caused by hormonal and nutritional imbalances, stress, and hypoxia (Reviews: Seelig, 1972; Seelig and Heggtveit, 1974).

It is important to note that the proposal that magnesium deficiency is a contributory factor in cardiovascular disease does not negate the role of high fat intakes (which interfere with magnesium absorption). Also, the theories implicating the fatty streak as an early infantile atherosclerotic lesion do not preclude the theories that elastica degeneration is one of the earliest arterial lesions. Lipid droplets are seen in conjunction with damaged elastica (Duff and McMillan, 1951) and have been correlated with elastica degeneration (Pickering, 1963; Zugibe, 1963). Furthermore, elastica degeneration predisposes to lipid deposition (Kramsch *et al.*, 1970, 1971). The papers that stress the changes in the musculoelastic layers of the arteries of infants as the earliest signs of arteriosclerosis support the premise that magnesium deficiency during the perinatal period, and factors that increase magnesium loss then and in early childhood, can contribute to the pediatric origins of cardiovascular

disease, since comparable changes are seen in magnesium deficiency (Review: Seelig and Haddy, 1976/1980).

5.1. Magnesium and Lipid Interrelationships

5.1.1. Influence of Fat on Magnesium Retention (Man)

Because excess (saturated) fat has been considered a major contributory factor in atherosclerosis and ischemic heart disease, and experimental and epidemiologic studies implicate magnesium deficiency *(infra vide)*, evidence of interrelationships between fat and magnesium is considered first.

5.1.1.1. Dietary Fat and Magnesium Balance

Evidence was obtained early that diets rich in fat interfere with magnesium absorption. In 1918, Sawyer *et al.* performed metabolic balance studies with 2 boys, 5 and 8 years of age, in which they explored the effects of fat intake on retention of calcium and magnesium. Even though their magnesium and calcium intakes were lower than in their normal diet, increasing the fat intake resulted in their excreting more of the divalent cations in both feces and urine. In a study of mineral balance of 4 young women on controlled magnesium-rich diets (800 mg/day), substitution of butter for vegetable fat resulted in retention of more magnesium (Bogert and Trail, 1922). On lower intakes of magnesium (320–350 mg/day), 6 young men given controlled diets containing 10–30% linoleic acid tended to be in negative magnesium balance while on the fatty-acid-supplemented diet (Irwin and Wiese, 1961). More extensive metabolic balance studies confirmed the interference by unsaturated fatty acids with magnesium retention in 19 young men on typical American intakes of magnesium, averaging 300–400 mg/day or 3.8–6.3 mg/kg/day (Hathaway, 1962). Magnesium, calcium, and phosphorus balances were calculated for ten 5-day periods, during which the diets were supplemented with linoleic acid at 9–10% and a subsequent increase in fatty acid to 20–30%. Most of the subjects were in probable magnesium equilibrium on the low-fat diets, considering balance to fall between 0 and +18 [the sweat loss of magnesium, that averages 18 mg/day (Seelig, 1964) not being allowed for in the figures given (Hathaway, 1962)]. When the fat intake was increased, although the magnesium intakes remained approximately the same, most retained less magnesium (Fig. 5-1). Only 1 of the 19 men remained in strongly positive magnesium balance on the high fat intake. Of 11 who were in ± magnesium balance during the low fat intake, 6 showed essentially no change on high fat, and 5 went into negative magnesium balance. Two, who were in slightly positive magnesium balance on low fat, dropped to no retention on high fat. Of five who were in strong negative balance on the low-fat diet, four continued to lose substantial amounts of magnesium when the fat intake was increased, and one lost less. Thus, 11 of the 19 subjects lost more magnesium on the high- than on the low-fat diets.

In a 5-day metabolic study of five normal medical students given a liquid diet, such as that given to preoperative peptic ulcer patients (that delivered 138 g of fat,

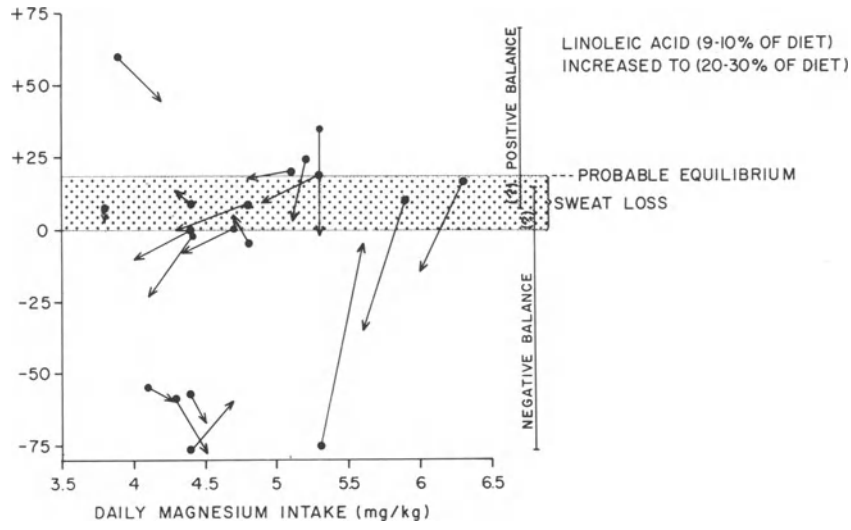

FIGURE 5-1. Magnesium balance related to intake of linoleic acid: young college students. (Derived from Hathaway, 1962.)

predominantly from whole milk and cream, and that provided only about 200 mg of magnesium daily), there was an average daily loss of 16 mg of magnesium (Macbeth and Mabbott, 1964). This amount of dietary fat is equivalent to that of the typical American diet, comprising about 40% of the daily calories (de los Rios, 1961). This liquid diet differed from that given to the young men on the linoleic acid diet (Hathaway, 1962) in that the ratio of calcium to magnesium was 9:1, rather than 2:1.

Metabolic balance studies in rats on low- and high-fat diets have also shown that increasing the fat intake decreases the amount of magnesium absorbed from the gut (Olson and Parker, 1964; Tadayyon and Lutwak, 1969).

5.1.1.2. Steatorrhea and Magnesium Loss

Diseases that interfere with fat absorption, thereby resulting in high concentrations of fat in the intestinal lumen, interfere with magnesium absorption in several ways. Insoluble complexes of the fats and magnesium and calcium prevent their transit across the intestinal membranes, in conditions such as celiac disease or sprue, and in the steatorrhea that develops after gastrointestinal resections. [Bowel resections or bypasses further contribute to magnesium depletion by shortened transit time, decreased absorption area, and decreased enzymatic lipolysis (Opie *et al.*, 1964).]

5.1.1.3. Dietary Fat and Blood Lipids (Man)

Despite the evidence that fat interferes with magnesium absorption, and that steatorrhea has caused hypomagnesemia and acute and subacute magnesium-deple-

tion syndrome, the short-term studies of the effect of high fat intakes on serum magnesium have shown no effect. For example, Macbeth and Mabbott (1964), who found that young men, on a "Sippy-like" ulcer liquid diet for five days, who were in negative balance, maintained normal serum magnesium levels (1.9 ± 0.34 mEq/liter). Studies with older (42–62 years of age) schizophrenic patients on diets delivering 34, 65, and 134 g of fat (each patient given each of the diets for two-week periods in different sequences) showed no change in serum magnesium levels on the different diets, though serum cholesterol levels fell on the low-fat diets (de los Rios, 1961).

The epidemiologic studies of residents of hard- and soft-water cities, which consider the fat intakes, the magnesium and calcium content of the water supplies, and serum lipid and magnesium and calcium levels (Bierenbaum *et al.*, 1973), provide interesting insight into the protective effect of hard water against sudden death from ischemic heart disease *(supra vide)*. Comparison of these parameters in hard-water American and English cities (Omaha, Nebraska, and London) with soft-water American and Scottish cities (Winston-Salem, North Carolina, and Glasgow) provides data that implicate the cations more than the fat ingested in the substantially lower cardiac death rates in Nebraska and in London than in the soft-water cities of southeastern United States and Glasgow (Review: Seelig and Heggtveit, 1974, and *supra vide*). For example, there was no significant difference in the percentages of those in Omaha and Winston-Salem (51.5% and 47.4%) who ingested diets high in fat, and in their serum cholesterol, triglycerides, and phospholipids. The tested residents of Glasgow, 72.8% of whom ate diets high in fat, had essentially the same serum lipid levels as did the tested London residents, only 28.2% of whom ate high-fat diets. Nonetheless, the serum cholesterol and triglyceride levels of Glasgow residents were the lowest of all the four cities. Also, residents of both hard-water cities had higher serum cholesterol than did those of their paired soft-water cities ($p \leq 0.05$). In evaluating the comparable serum levels of magnesium in both American cities, but the significantly higher serum magnesium in London than Glasgow, the noted common use of water softeners in Omaha (but not in London) should be considered. Residents of both American cities had significantly higher serum calcium levels (10.37 in Omaha, 9.59 in Winston-Salem) than did those in Britain (8.57 in London, 8.7 in Glasgow). The possibility that this is a reflection of more milk and vitamin D ingested by adults in the United States than in Britain should be considered, since the calcium content of London water was 2–3 times as high as that in the American cities.

With these data in mind, it is not surprising that there has been disagreement as to correlation of serum magnesium and cholesterol levels in patients with cardiovascular disease, or in populations at different risk.

5.1.1.4. Serum Magnesium and Cholesterol Levels in Cardiovascular Patients and High-Risk Populations

Bersohn and Oelofse (1957) and Bersohn (1958) correlated the lower serum cholesterol and slightly higher magnesium levels in Bantus than in white South Africans, with the lower incidence of arteriosclerosis and the higher dietary intake

of magnesium of the Bantus. They analyzed the serum magnesium levels of Europeans with low to high serum cholesterol levels and found that, although there was overlap of serum magnesium values, the mean magnesium level of those with low serum cholesterol (mean = 170 mg/100 ml) was higher (1.7 mEq/liter) than was that of patients with hypercholesterolemia (cholesterol: 310–586 mg/100 ml; magnesium: 1.4 mEq/liter). In an Australian study comparing serum cholesterol and magnesium levels in several groups of aborigines and Europeans, Charnock *et al.* (1959) confirmed the lower serum cholesterol levels of the aborigines (who have a low incidence of cardiovascular disease) than of the Europeans and found significant differences ($p \leq 0.001$) between serum magnesium levels of the aborigines (1.7 mEq/liter) and the Australians living in Adelaide (1.2 mEq/liter). Another group of Australians, living in a northern area (Alice Springs) one thousand miles away, had high mean serum magnesium levels (1.9 mEq/liter) and the highest mean serum cholesterol (314 mg/100 ml) of all the groups tested. Thus, the correlation between magnesium and cholesterol levels was not consistent. (The nature of the water of Alice Springs was not given.) It was interesting that there was no difference in serum magnesium (1.3 mEq/liter) and cholesterol levels (286; 281 mg/100 ml) in ischemic heart disease patients and age-matched European controls in Adelaide.

D. F. Brown *et al.* (1958), noting the report by Bersohn and Oelofse (1957) *(supra vide)* and that by Malkiel-Shapiro *et al.* (1956) that parenteral administration produced clinical improvement and lowered β-lipoprotein levels in patients with myocardial infarction (MI), studied serum magnesium–lipid relations in MI patients and in middle-aged controls. They found no correlation between serum magnesium and lipid levels, and no significant difference between the patients and the controls. Similar negative findings have been reported by others in studies of patients with cardiovascular disease and hyperlipidemia (Hyatt *et al.*, 1966; Murnaghan *et al.*, 1969; Rotman *et al.*, 1971/1973).

On the other hand, Jankelson *et al.* (1959), who compared serum magnesium and lipid fractions of atherosclerotic patients and controls, found that although total cholesterol levels were the same in both groups, there were differences in magnesium and lipoprotein levels. The average serum magnesium level was 1.4 mEq/liter in 23 atherosclerotic patients and 1.6 in 12 healthy controls (in third and fourth decades of life). The β-lipoproteins were 11.5 in patients and 8.5 in controls; the α-lipoproteins were 5.3 in patients and 2.2 in controls. Six of the atherosclerotic patients were alcoholics; all had normal cholesterol levels, but 4 had high β-lipoprotein and all had higher than control α-lipoprotein values; 4 had very high levels. There was not good correlation, however, of low serum magnesium levels with high lipoproteins. Three with arteriosclerotic heart disease, and/or cerebral thrombosis, respectively, had hypomagnesemia (0.7, 0.7, and 1.3 mEq/liter) and hyper-β-lipoproteinemia (8, 13.4, and 9). But 2 with comparable disease and high β-lipoproteins (12.5 and 14.3) had normal serum magnesium (1.7 and 2.0 mEq/liter). One with cerebral thrombosis had normal magnesium and lipid levels. High serum cholesterol levels (288 mg/100 ml) and low serum magnesium levels (1.5 mEq/liter) were seen in 25 patients with acute MI a week after the infarction, as compared with the average levels in 50 controls (cholesterol: 210; magnesium: 2.1 mEq/liter) and in 15 old MI cases (cholesterol: 238; magnesium: 1.9) (Nath *et al.*, 1971/1973). The mag-

nesium levels rose during the next two weeks to normal (1.9 mEq/liter). Patients with angina pectoris, in this series, had high cholesterol levels (278) but normal serum magnesium values (2.0 mEq/liter). Rangam and Gupta (1961) found that among 44 patients with hypercholesterolemia, 80% had hypomagnesemia; among 52 with high lipid phosphorus levels, 75% had low serum magnesium levels. Those with normal cholesterol levels, however, also had a high incidence (54%) of hypomagnesemia in this series.

A brief abstract reports highly significant ($p \leq .001$) correlations between magnesium and high cholesterol and low-density lipoproteins in a survey of 32 random subjects 40–60 years of age (Mondschein, 1974). Over half of the magnesium values were below the normal range; none was above.

5.1.1.5. Clinical Use of Magnesium in Cardiovascular Disease with Hyperlipidemia

Many of the attempts to determine whether high serum cholesterol levels correlated with low magnesium levels in patients with cardiovascular disease derived from the clinical reports that parenteral magnesium administration was of value in treating patients with myocardial infarcts (MI), coronary insufficiency, and/or peripheral arteriosclerosis. Malkiel-Shaprio *et al.* (1956) first reported lowering β-lipoproteins in patients with coronary insufficiency, with the use of intramuscular (i.m.) $MgSO_4$, begun at the time of an acute attack of coronary thrombosis or during acute coronary insufficiency. The regimen employed by Malkiel-Shapiro (1958) for 25 years involved deep i.m. injections of 0.5–2.0 ml of 50% $MgSO_4$ on alternate days, and at longer intervals (to twice weekly) as the condition improved. Patients who had recently recovered from an MI or who suffered angina of effort were usually given 12 i.m. injections of $MgSO_4$ at 5-day intervals, which was repeated after 4–6 months if they had benefited. These physicians stated that patients with more advanced disease seemed to have the most striking improvement. In the earlier studies (Malkiel-Shapiro *et al.*, 1956), patients on magnesium therapy were given no anticoagulants. Subsequently, concurrent use of small doses of heparin (5000 units daily) and i.m. $MgSO_4$ (0.5–1 ml 50% solution) once weekly were found useful in the maintenance of patients who have recovered from an acute MI (Malkiel-Shapiro, 1958; Malkiel-Shapiro *et al.*, 1960). After the 1956 report of this group, clinical trials were undertaken in South Africa (Teeger, 1958; Agranat 1958; Marais, 1958) and Australia (R. Parsons, 1958; R. Parsons *et al.*, 1959, 1960, 1961), and there was clinical verification of much that had been claimed. Agranat (1958) reported a 44% improvement rate with the use of $MgSO_4$ injections to patients with chronic IHD. R. Parsons (1958) reported briefly that 3 injections of 1 ml 50% $MgSO_4$ weekly for a month to IHD patients resulted in reversal of low lecithin/cholesterol ratio, lowering of the β-lipoprotein levels with elimination of the pre-β- band, and reduction of plasmin inhibition. In a detailed report, R. Parsons *et al.* (1959) described treatment of patients with angina but no ECG evidence of MI, and of patients with ECG evidence of MI with or without angina. They found that 2-ml doses of 50% $MgSO_4$, given i.m. every 5 days (until 12 doses were given), were more effective than were the 1-ml doses. Patients with acute MI were also given heparin

TABLE 5-1. Serum Magnesium, Lipid, and Plasmin Changes in Patients with Ischemic Heart Disease Treated with Magnesium[a]

	Decreased (%)	No change (%)	Increased (%)
Lecithin	34	12	54
Cholesterol	82	4	14
Lecithin/Cholesterol	0	14	86
α-Lipoproteins	40	28	32
β-Lipoproteins	66	28	6
Plasmin Activation	18	38	44
Plasmin Inhibition	62	34	4
Magnesium	8	0	92

[a] From PS Parson, I Butler, and EP Sellars (1959).

for the first 3 days of treatment. Comparison of the results of this regimen with that obtained the previous year when only anticoagulants were used were striking. Of over 100 patients given the magnesium therapy, one-third of whom had had acute MI, there was only one death. Among almost 200 patients treated with anticoagulants alone, 60 died. The biochemical changes (Table 5-1) show the improvement in lecithin/cholesterol ratio, the decrease—particularly in β-lipoproteins—and in plasmin inhibition produced by the magnesium therapy. In 1960, Parsons *et al.* published confirmation of the observation (Malkiel-Shapiro, 1958) that combination of low dosage heparin with i.m. magnesium therapy was even more effective in speedily reducing β-lipoproteins and total lipids to normal levels. They recommended that patients with acute MI should be given heparin (15,000 units every 6 hours for 3 days), with an initial dose of 2 ml 50% $MgSO_4$ i.m. Then low-dosage (5000 units) heparin and 2 ml 50% $MgSO_4$ were given three times weekly for 6 weeks, and once weekly subsequently.

Application of this regimen to patients with angina, MI, or peripheral arterial disease (incipient gangrene, ischemic leg ulceration, Raynaud's disease, and intermittent clandication) has been reported to produce clinical improvement and to lower serum cholesterol levels (S. Browne, 1961, 1963, 1964a,b). Savenkov *et al.* (1971) have also reported that treatment with a preparation containing magnesium adipate and magnesium nicotinate (in tablet or ampoule form for i.v. or i.m. administration) has been useful in the treatment of 54 patients with coronary, cerebral, and (in 21 cases) peripheral atherosclerosis. Treatment was given for 20 days parenterally (18 patients), orally (20 patients), or parenterally for half the course, followed by oral administration (16 patients). The clinical response was considered good in 22 instances, satisfactory in 16, and effective in 10. The total serum cholesterol was obtained in 41 patients (average = 284 ± 16.9 mg/100 ml). The level decreased in 29 patients, did not change in 9, and rose by 24 mg/100 ml in 3. In the entire group, there was an average decrease of 17.5%.

A magnesium–aluminum–siliconate preparation was given in fairly high dosage (2–3 g/day) to hyperlipemic patients without (Table 5-2A) and with (Table 5-2B) moderate to severe manifestations of cerebral, coronary, or peripheral arterial disease (Lieber, 1961). The most reduction was in the esterified cholesterol fraction,

TABLE 5-2. Serum Lipids in Patients with Hyperlipidemis and Arteriosclerosis: Response to Magnesium Preparations[a]

Category of patients	Number of cases	Treatment condition	Total lipids	Lipid levels (mg/100ml)							
				Lipoproteins			Cholesterol			Phospholipids	
				α	β	β/α	Total	Ester	Free	Lecithin	Free
A. Hyperlipidemia	(39)	(Initial values)	1037 ± 912	17.8 ±	82.3 ± 41	4.8 ± 1	256 ± 31	1850 ± 25	71 ± 13	13 ± 1	321 ± 160
	9	After 30–40 days Mg[b]	1050 ± 287	19 ± 5	81.6 ± 16	4.4 ± 1	260 ± 30	182 ± 19	77 ± 10	12.8 ± 2	320 ± 21
	13	After 50–60 days Mg	881 ± 19	20 ± 1	79 ± 10	3.8 ± 0.9	247 ± 26	175 ± 15	71 ± 7	12 ± 0.3	323 ± 21
	12	After 90–120 days Mg	932 ± 48	23.7 ± 3	76 ± 3	3.2 ± 0.6	237 ± 44	172 ± 25	47 ± 27	12 ± 4	304 ± 46
	5	After 150–200 days Mg	869 ± 101	25 ± 1	74 ± 2	3 ± 0.5	213 ± 10	161 ± 9	70 ± 27	11 ± 0.2	276 ± 21
B. Occlusive A. S. (moderate to severe)	(14)	(Initial values)	1098 ± 9	20.7 ± 3.5	65.5 ± 15	3.5 ± 0.7	263 ± 34	187 ± 23	76 ± 18	12.6 ± 10	325 ± 36
	4	After 20–20 days Mg[b]	1343 ± 471	23.5 ± 3	76.5 ± 3	3 ± 0.8	258 ± 15	188 ± 45	70 ± 7	13.5 ± 1.5	331 ± 25
	5	After 45–70 days Mg	808 ± 196	23 ± 3	77 ± 8	3.4 ± 0.7	145 ± 30	211 ± 40	64 ± 15	12 ± 1.2	310 ± 25
	5	After 90–150 days Mg	973 ± 406	25.5 ± 6	74.8 ± 6	3 ± 1	227 ± 48	164 ± 27	58 ± 20	11.4 ± 6	276 ± 3
C. Hyperlipidemia	(7)	(Initial values)	883 ± 48	20.7 ± 2	79.2 ± 3	3.9 ± 2	225 ± 27	184 ± 17	46 ± 8	11.4 ± 0.7	287 ± 20
	5	After 15–25 days Mg[c]	833 ± 41	27.9 ± 135	72 ± 3	2.6 ± 0.7	215 ± 22	149 ± 30	46 ± 5	11.4 ± 0.8	285 ± 21
	2	After 45–80 days Mg	816 ± 14	25.7 ± 0.2	74.2 ± .2	2.8 ± 0.1	183 ± 31	167 ± 3	57 ± 26	11	281 ± 2
D. Hyperlipidemia + moderate to severe clinical signs	(15)	(Initial values)	951 ± 131	19.5 ± 3.5	78.2 ± 4.5	4.5 ± 0.3	257 ± 44	196 ± 40	48 5	13.5 ± 1.8	304 ± 16
	9	After 15–35 days Mg[c]	961 ± 220	23.7 ± 4.5	76.2 ± 4.5	3.3 ± 0.3	243 ± 40	185 ± 14	52 ± 16	12 ± 0.3	301 ± 24
	6	After 40–70 days Mg	982 ± 982	24.8 ± 6	76 ± 4	3.3 ± 0.6	239 ± 43	184 ± 25	51 ± 15	12 ± 1	300 ± 40

[a] Derived from II Lieber (1961).
[b] As magnesium–aluminum–hydrosiliconate (2–3 g/day, p.o.).
[c] As magnesium nicotinate (100 mg/day, p.o.).

an interesting finding in view of the high levels of cholesterol esters in magnesium-deficient dogs (Kruse *et al.*, 1933) and rats (Savoie and Delorme, 1976/1980). The ratio of β/α-lipoproteins fell increasingly with the duration of administration of the magnesium preparation, and to a greater degree in group A than group B. The low-dosage magnesium nicotinate preparation was given to patients with lesser degrees of hyperlipidemia, and produced less striking changes, but in the same direction (Table 5-1C, D) (Lieber, 1961). The tendency toward magnesium-induced decreased β-lipoprotein levels is reminiscent of comparable findings in magnesium-supplemented rats on atherogenic diets (*infra vide*).

A brief abstract of a long-term (19-month) double-blind study of 35 patients given either oral $MgCl_2$ and KCl (1 mEq/kg/day) or placebo, reported that serum β-/α-lipoproteins were 10% lower in the treated group than in the placebo group (Haywood and Selvester, 1962). The dose-limiting effect of side effects was considered a likely explanation of the failure to reduce the lipids further. Smaller doses of magnesium given in complexed or chelated form were reported to lower the elevated β-fraction somewhat, but not to lower the total cholesterol levels; when the magnesium was stopped the β-fraction rose to pretreatment levels (A. Steiner, 1962, 1963). In the latter study, β-vitamins were also given.

Rademeyer and Booyens (1965), having shown that the maize meal dietary constituent of the Bantus had a hypocholesterolemic effect in rats, which they attributed to its high magnesium content and to its interference with fat absorption, demonstrated that supplementation with maize meal of diets of hyperlipemic whites raised their serum magnesium and lowered their serum cholesterol levels (Booyens *et al.*, 1966).

5.1.2. *Blood and Cardiovascular Magnesium and Cholesterol in Experimental Dietary Atherogenesis and Cardiopathies*

The conflicting clinical reports as to the relationships of serum magnesium and lipid levels, and their meaning in cardiovascular disease, call for evaluation of magnesium–lipid interrelationships in experimental atherogenesis. In particular, because of the poor correlation between serum lipid levels and protection against heart disease in hard-water areas (Bierenbaum *et al.*, 1973), and because magnesium administration has been claimed to be beneficial in overt clinical cardiovascular disease, animal data deserve careful scrutiny.

Among the numerous studies of atherosclerosis induced by fat, cholesterol, and cholic-acid-loading of animal diets, few have included determination of magnesium levels. The early magnesium-deficiency studies by Kruse *et al.* (1933) showed that young dogs on an atherogenic diet low in magnesium (.08% of diet) and containing butter fat (8% of diet), exhibited no change in total blood lipids, little or no change in free cholesterol, a drop in fatty acids, but a substantial rise in esterified cholesterol. As the magnesium level dropped, the percentage of esterified cholesterol rose. The young dogs on a magnesium-free, but otherwise well-balanced, diet, which delivered no lipid other than corn oil, were found by Vitale *et al.* (1961) to develop neither elevation of blood cholesterol nor atheromatous plaques. Bunce *et al.* (1962a,b) demonstrated that increasing the magnesium intake from 80

to 180 ppm, in dogs fed 20%-animal-fat diets, prevented the aortic lesions seen in dogs on the lower magnesium intake, but allowed for a slight further rise in serum cholesterol.

The atherogenic diet fed to rats (Vitale *et al.*, 1957a,c,d,e; Hellerstein *et al.*, 1957, 1960) produced marked hypercholesterolemia (639–808 mg/100 ml) that was not lowered by increasing the magnesium intake, even though early arteriosclerotic lesions were diminished (Vitale *et al.*, 1957d,e; Nakamura *et al.*, 1960). In rats on the atherogenic diet, also high or low in protein (Vitale *et al.*, 1957c) or calcium (Vitale *et al.*, 1959), increasing the magnesium content caused a further rise in serum cholesterol. A high intake of both magnesium and calcium, reduced the sudanophilia of the hearts to 4.0 from the high value of 8.3, but exerted little influence on serum lipids (Table 5-3). Increasing the magnesium intake of rats on low calcium intake substantially lowered the β-lipoproteins. A high magnesium intake slightly lowered the serum cholesterol and more profoundly lowered the lipoproteins of rats on high and low fat intakes, whether the fats were saturated or unsaturated (Hellerstein *et al.*, 1960: Table 5-4). No cardiac sudanophilia developed, unless cholesterol and cholic acid were added to the diet. The markedly elevated plasma cholesterol, seen in rats also given cholesterol and cholic acid, was actually increased on the higher Mg intakes, although the cardiac lipid deposition in the rats on saturated fats and high Mg was reduced. Altering the Mg intake did not notably affect the lesser heart scores of rats on high intakes of unsaturated fat (Table 5-5).

TABLE 5-3. Effect of Dietary Magnesium and Calcium on Serum Cholesterol and Lipoproteins, and on Heart Sudanophilia in Rats on Atherogenic Diet[a]

Diet[b]	Serum			Sudanophilia (heart score)
	Cholesterol (mg/100 ml)	α-Lipoprotein	β-Lipoprotein	
No cholesterol or cholic acid				
Low calcium				
Low magnesium	108	7.3	10.0	0.0
High magnesium	114	6.6	6.1	0.0
High calcium				
Low magnesium	117	2.4	4.7	0.0
High magnesium	115	3.8	5.7	0.0
With cholesterol (1.0 g/100 g) + cholic acid (0.3 g/100 g)				
Low calcium				
Low magnesium	515	3.5	26.1	4.7
High magnesium	705	2.4	4.7	3.0
High calcium				
Low magnesium	748	2.1	35.9	8.3
High magnesium	818	3.7	29.7	4.0

[a] Adapted from Vitale *et al.* (1959).

[b] Casein (10 g/100 g); saturated cottonseed oil (20 g/100 g); glucose (58.4 g/100 g); salt mixture, without Ca or Mg (15 g/100 g); cellulflour (5 g/100 g) + vitamins. Low calcium = 600 mg/100 g; high calcium = 1200 mg/100 g; low magnesium = 24 mg/100 g; high magnesium = 192 mg/100 g.

TABLE 5-4. Effect of High and Low Saturated and Unsaturated Fat Intakes and of Magnesium on Serum Lipids in Rats[a]

Dietary fat[b, c]	Serum magnesium (mg/100 ml)		Serum cholesterol (mg/100 ml)		Serum lipoproteins			
					α		β	
	Satur.	Unsatur.	Satur.	Unsatur.	Satur.	Unsatur.	Satur.	Unsatur.
Low fat intake (5%)								
Low magnesium	1.08	1.25	105	127	9.7	6.9	11.7	8.8
Moderate magnesium	2.21	2.03	99	138	8.5	10.0	10.3	10.6
High magnesium	2.56	1.91	83	116	4.1	7.3	4.8	7.7
High fat intake (20%)								
Low magnesium	1.51	0.96	115	115	15.9	8.1	11.8	8.5
Moderate magnesium	1.89	1.99	113	123	16.3	6.9	12.6	5.4
High magnesium	2.09	1.95	97	102	7.7	4.0	6.3	4.8

[a] Adapted from Hellerstein *et al.* (1960).
[b] Dietary fat: saturated—hydrogenated cottonseed oil; unsaturated—corn oil.
[c] Low magnesium = 24 mg/100 g; moderate magnesium = 96 mg/100 g; high magnesium = 192 mg/100 g.

The elevation of heart scores of rats on low unsaturated fat diets when their magnesium intake was increased requires elucidation. Vitale *et al.* (1959) and Hellerstein *et al.* (1957, 1960) suggested that magnesium might protect against lipid deposition in the cardiovascular system by means of its effect on lipoprotein metabolism. They demonstrated that further increasing the intakes of cholesterol to 3% and cholic acid to 1%, of rats on 20% unsaturated fat, increased serum cholesterol levels

TABLE 5-5. Effect of Saturated and Unsaturated Fats and of High and Low Magnesium Intakes on Serum Cholesterol and Heart Sudanophilia in Rats on Atherogenic Diet[a]

Dietary fat[b, c]	Serum magnesium (mg/100 ml)		Serum cholesterol[d] (mg/100 ml)		Heart score	
	Satur.	Unsatur.	Satur.	Unsatur.	Satur.	Unsatur.
With cholesterol (1.0 g/100 g) + cholic acid (0.3 g/100 g)						
Low fat intake (5%)						
Low magnesium	0.88	0.98	724	397	9.0	3.6
Moderate magnesium	2.29	1.89	794	341	8.8	2.8
High magnesium	2.22	2.15	821	385	6.2	5.3
High fat intake (20%)						
Low magnesium	1.08	1.11	1086	210	6.0	2.0
Moderate magnesium	2.08	1.99	653	270	3.8	2.3
High magnesium	1.91	2.14	1085	355	4.1	2.3

[a] Adapted from Hellerstein *et al.* (1960).
[b] Dietary fat: saturated—hydrogenated cottonseed oil; unsaturated—corn oil.
[c] Low magnesium = 24 mg/100 g; moderate magnesium = 96 mg/100 g; high magnesium = 192 mg/100 g.
[d] Serum lipoproteins were 2.7–7.5 cm^2 for the α-lipoproteins and 20–50 cm^2 for the β-lipoproteins (by paper electrophoresis). Effect of Mg not demonstrable because of imprecision of method.

only slightly (to 440 mg/100 ml), but increased the heart scores of rats on low magnesium intake to 5.2. High magnesium intake protected against this increased heart score (Table 5-6). Increasing the magnesium intake of rats on atherogenic diets, given alcohol or water to drink, also resulted in higher serum cholesterol levels, but less cardiovascular sudanophilia (Vitale *et al.*, 1957a). Nakamura *et al.* (1960, 1966) showed that the long-term feeding of 192 mg/100 g of magnesium to rats on this atherogenic diet 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 two months on the magnesium-supplemented diet.

In contrast to the results in the foregoing studies with hypercholesterolemic semisynthetic diets, the high blood cholesterol produced in rats fed whole milk (containing 4 g butter fat/100 ml milk) alone or with added cholesterol, was corrected by adding $MgSO_4$ to the diet (Mullick and Kakkar, 1963). It seemed possible that formation of insoluble compounds of the milk fat and magnesium might have prevented absorption of the excess fat. However, in another report, magnesium salt given intramuscularly also lowered the serum cholesterol (Kakkar and Mullick, 1963).

Rademeyer and Booyens (1965) explored the effect of butter fat versus sunflower-seed oil on the serum magnesium and cholesterol levels of rats fed a semisynthetic low magnesium diet similar to that used by Vitale's group *(supra vide)*. They found that the addition of 25% butter fat to the diet lowered the serum magnesium from 3.3 to 2 mEq/liter and raised the serum cholesterol from 65.8 to 81.6 mg/100 ml over a 4-week period ($p \leq 0.001$). The serum magnesium did not fall on addition of 25% sunflower-seed oil, nor did the serum cholesterol rise. An equal amount of meat-fat drippings caused a lesser fall in serum magnesium than did the butter fat, and lesser but significant rise in serum cholesterol. Substituting sunflower-seed oil for butter in the group that had been fed the butter-supplemented diet for 4 weeks affected neither the depressed serum magnesium nor the elevated

TABLE 5-6. Protective Effect of High Magnesium Intake Against Cardiac Lipid Deposition in Rats on High Cholesterol + Cholic Acid Intakes[a]

Atherogenic diet[b]	Serum cholesterol mg/100 ml	Heart score
With 1% cholesterol and 0.3% cholic acid		
Low magnesium[c]	210	2.0
High magnesium	355	2.3
With 3% cholesterol and 1.0% cholic acid		
Low magnesium[c]	440	5.2
High magnesium	385	2.9

[a] Adapted from Hellerstein *et al.* (1960).
[b] Dietary fat = 20% corn oil.
[c] Low magnesium = 24 mg/100 g; high magnesium = 192 mg/100 g.

serum cholesterol, but substitution of maize meal for glucose caused a rise in magnesium and a fall in cholesterol within a week. Maize meal (a major dietary constituent of Bantus) was used in this study in an effort to determine why Bantus have a lower serum cholesterol and higher serum magnesium level, as well as a lower incidence of arteriosclerosis than do South African whites (Bersohn and Oelofse, 1957).

Hungerford and Bernick (1976/1980) have recently reaffirmed the lack of alteration of plasma magnesium in rats on synthetic atherogenic diets, and elucidated the histologic arterial changes produced by an atherogenic or magnesium-deficient, or combined high-fat low-magnesium diet. They showed the further increase in serum cholesterol produced when rats on atherogenic diets were also magnesium deficient.

Rabbits on a hypercholesterolemic diet for 24 weeks showed a sharp drop in serum magnesium (and calcium) at 6 weeks. The hypomagnesemia persisted for 6 more weeks and then tended to rise (Rangam and Gupta, 1961). Intravenous $MgSO_4$ injection (2 ml 5% solution) to such rabbits was found to lower serum cholesterol for 48 hours (Rangam and Gupta, 1962). Magnesium deficiency intensified the deposition of fat in the aortas of rabbits on atherogenic diets, lowered the level of serum triglycerides significantly ($p \leq 0.05$), but exerted little effect on total serum cholesterol (Nakamura *et al.*, 1965). Magnesium supplementation had little effect on serum aorta lipid levels in rabbits in one study (C. Adams *et al.*, 1964). Neal and Neal (1962) found higher serum phospholipid and triglyceride levels in rabbits on atherogenic diet when their drinking water contained magnesium than when they were given distilled water to drink, but they had less atherosclerosis when they were magnesium supplemented. Another group confirmed these observations. They found that administration of magnesium (as Mg Na_2 EDTA) had little effect on the hyperlipidosis of rabbits on atherogenic diet but reduced formation of atheromatous plaques (McCann *et al.*, 1962; Wartman *et al.*, 1967). The magnesium-deficient cebus monkeys on atherogenic diets, reported by Vitale *et al.* (1963), showed both elevated serum cholesterol values and marked intimal lipid deposition in the aorta, not seen in controls. A study of the response to [^{3}H]cholesterol, given intravenously to magnesium-deficient and control rats, showed that the tagged cholesterol was taken up and subsequently released more rapidly by the liver of magnesium deficient than control rats. As a result, there was an initially greater drop in serum [^{3}H]cholesterol and a greater subsequent rise in the magnesium-deficient rats; they also exhibited extracellular [^{3}H]cholesterol between the elastic lamellae and the smooth muscles in the aorta (Schmalbeck *et al.*, 1972).

The Mg- and KCl-free diet, containing animal fat, vitamin D, and sodium phosphates, which was contrived by Sos *et al.* (1964a,b,c) to be cardiopathogenic in several species, produced elevated serum cholesterol levels (Review: Seelig and Haddy, 1976/1980). A similar diet, designed to be thrombogenic, but that also produced cardiac necrosis in rats (Savoie, 1972a,b, 1975; Savoie *et al.*, 1973), produced a substantial rise in blood cholesterol levels, particularly in the esterified form (Savoie and Delorme, 1976/1980), a finding that recalls the early observation by Kruse *et al.* (1933) in dogs. Blood phospholipids were also increased, and blood magnesium levels were lowered. Magnesium supplementation of the atherogenic or

of the thrombogenic diet exerted little effect on most of the blood lipid fractions, raising some further and lowering some slightly but none to normal levels (Savoie and Delorme, 1976/1980). It is noteworthy that hypocholesterolemic agents (clofibrate, nicotinic acid, and conjugated estrogens) exerted no protective effect against the nonocclusive suppurative cardiac necrosis produced when Na_2 HPO_4 was added to the hyperlipemic thrombogenic diet. Only $MgCl_2$ was completely protective (Savoie, 1972b). Further work showed that the sodium phosphate addition accentuates the hypokalemia of the thrombogenic diet, but produces hypomagnesemia, and lowers the cardiac magnesium levels. More recently, Savoie and Delorme (1976/1980) found that the thrombogenic diet increased lipoprotein lipase activity, an effect not influenced by magnesium. On the other hand, the added phosphate lowered the cardiac lipase activity, and magnesium raised it, with resultant elevation of cardiac free fatty acid levels. Magnesium lowered the free cholesterol levels in the hearts of the rats on the cardiopathic diet.

5.1.3. Magnesium/Lipid/Catecholamine Interrelationships

Catecholamines have long been known to increase the blood levels of free fatty acids, whether by injection in animals (Dole, 1956; Bogdonoff *et al.*, 1961) or as a result of such stress as myocardial infarction (Kurien and Oliver, 1966; Kurien *et al.*, 1971; Oliver *et al.*, 1968; Editorials, *Lancet,* 1969a,b). The complex interrelationships of magnesium and catecholamines and corticosteroids have been surveyed by Wallach (1976/1980) and those of corticosteroids (which are also released by stressful situations) and magnesium by Massry and Coburn (1973). In the case of the catecholamines, depending on the time of testing and the test situation, they have both increased and decreased blood magnesium levels and decreased tissue (i.e., heart) magnesium levels.

Considered here are the blood lipid–magnesium interrelationships, as influenced by cold-stress, the acute alcohol-withdrawal syndrome, and the administration of catecholamines, which might provide some insight into the somewhat contradictory findings. Rayssiguier and Larvor (1976/1980) have recently reported that either fasting or exposure of shorn young sheep to cold temperatures causes comparable lipolysis to that produced by infusions of either epinephrine or theophylline. Hypomagnesemia accompanied the increase in free fatty acid levels in the blood, caused by each of the stimuli. Sodium nicotinate, which is antilipolytic, inhibited both the increase in free fatty acids in the blood and the decrease in blood magnesium. High blood levels of long-chain free fatty acids are also seen during the acute phase of alcohol withdrawal (Mays *et al.*, 1970) and the severity of the symptoms tends to be greater in those with higher levels of the fatty acids (Flink *et al.*, 1973, 1976/1980). Since such fatty acids can chelate magnesium, Flink *et al.* (1976/1980) propose that the signs of alcohol withdrawal may depend upon inactivation of magnesium by the fatty acids. They verified the elevation of free fatty acids in the blood of dogs induced to imbibe alcohol and suggested that reducing lipolysis during alcohol withdrawal might be useful in controlling the symptoms, which are often controllable by magnesium repletion (Flink *et al.*, 1954, 1957; Flink, 1956, 1969, 1976/1980).

The mobilization by catecholamines of free fatty acids and their inactivation of magnesium recall Browne's early (1964a,b) deduction that the clinical benefit reported from magnesium therapy of hyperlipemic patients with occlusive arterial disease might derive from magnesium–catecholamine interrelationships. He pointed out that magnesium inhibits catecholamine release from the adrenal medulla (Douglas and Rubin, 1961, 1963, 1964), and that smoking or nicotine infusions (to dogs) causes elevation of both serum free fatty acid levels and urinary excretion of catecholamines (Kershbaum and Bellet, 1964). The arrhythmia following clinical myocardial infarction might be related to the catecholamine-induced increase in circulating fatty acids that might be mediated by inactivation of serum magnesium. Perhaps more likely is the possibility that increased myocardial lipids, such as have been attributed to catecholamine lipid mobilization in rats injected with sympathomimetic agents (Ferrans *et al.*, 1964, 1969) and in electrolyte-steroid cardiopathy (Prioreschi, 1966), might be the result of inactivation by the intramyocardial fats of cellular magnesium. It is provocative, in this regard, that a direct correlation was made by Balazs *et al.* (1962) with the cardiotoxicity of isoproterenal in rats and the amount of excess body fat. The availability of more fat for lipolysis under stressful situations might explain the greater susceptibility of obese individuals to fatal ischemic heart disease.

5.1.4. Estrogen, Lipids, and Magnesium; Interrelationships with Arteriosclerosis and Thrombosis

5.1.4.1. Estrogen Therapy of Ischemic Heart Disease

The treatment of men with coronary insufficiency by estrogens is no longer advocated. Estrogens used to be administered in an effort to lower the β/α-lipoprotein ratio of these men to that of young women (Barr, 1955; Oliver, 1960) because of the sex difference in the incidence of ischemic heart disease. Despite success in lowering the β- and raising the α-lipoprotein levels by giving estrogens (Barr *et al.*, 1952; Townsend *et al.*, 1952; Gertler *et al.*, 1953, Steiner *et al.*, 1955; R. W. Robinson *et al.*, 1956; Voyles and Evans, 1961), there has not been satisfaction that a sufficiently suppressive effect is exerted on recurrence of cardiovascular accidents to justify the unpleasant side effects (Steiner *et al.*, 1955; Oliver, 1962; Robinson *et al.*, 1963).

The effect of estrogens on blood coagulation may provide a possible explanation of their failure to achieve benefit in patients who had suffered a myocardial infarction, a condition associated with increased coagulability of the blood shortly after the event (McDonald and Edgill, 1957, 1959; Katz *et al.*, 1963). Estrogens have long been known to increase the coagulability of blood, an attribute that has been used to stop bleeding [e.g., after tonsillectomies (S. Fox, 1960) and to control epistaxis (E. Blackburn, 1963)]. This activity, however, seems relevant to the correlation of thromboses and infarctions with the use of estrogen-containing oral contraceptives (Inman *et al.*, 1970; Coronary Drug Project Report, 1973a; Editorial, *Lancet,* 1977; Goldsmith and Johnston, 1979).

If one accepts the premise that formation of mural thrombi is a pathogenic mechanism in atherogenesis (Duguid, 1946; T. Crawford, 1959; Astrup, 1959; McDonald, 1959; Pilgeram, 1961; Pickering, 1963. A. Katz *et al.*, 1963), the enhancement of intravascular coagulation by estrogens should result in a higher, rather than the lower incidence of cardiovascular disease in premenopausal women than in men.

5.1.4.2. Estrogen, Cardiovascular Effects, and Magnesium

It was speculated (Seelig, 1964) that the common denominator between the low incidence of ischemic heart disease in men from the Orient (where the intake of saturated fat is low) and in young women might be magnesium. The substantially higher dietary intakes of magnesium in the Orient, and the better retention of magnesium by young women than young men on the customary marginally adequate magnesium intake of the Western world, suggested that the adequacy of magnesium might be the protective factor against IHD. If the effective retention of magnesium by women reflects its affinity, not only to target tissues such as those involved in the reproductive process and to bone (Walaas, 1950; Csapo, 1956; Best and Pickles, 1965; N. Goldsmith, 1971) but to the cardiovascular system, that might elucidate the greater resistance of premenopausal women than of older women and of both young and older men to cardiovascular disease. Thus far, experimental data verifying the greater resistance of females than males to cardiopathic agents have not elucidated the possible role of cardiovascular magnesium levels. One can draw some inferential conclusions, but definitive work remains to be done. For example, female dogs and rabbits are more resistant than are males to digitalis-induced arrhythmias (Grinnell and Smith, 1957; Rodensky and Wasserman, 1964). Castrated females are as susceptible as are males to digitalis toxicity; estrogen replacement (2 mg/day) markedly improves their resistance to arrhythmias, but not to the extent seen in estrus (Table 5-7A, Grinnel and Smith, 1957). High-dosage estrogen has been almost fully protective against the myocardial necrotic lesions produced by phosphate and corticoids and by digitalis overdosage and has protected against myocardial necrosis caused by dihydrotachysterol (Table 5-7B, Selye, 1970a). It is thus of interest that digitalis toxicity is increased by magnesium deficiency (Vitale *et al.*, 1963), that digitalis increases the renal excretion of magnesium (Kupfer and Kosofsky, 1965), and that magnesium is useful in digitalis toxicity (Zwillinger, 1935; Szekely and Wynne, 1951; J. Stanbury and Farah, 1960; Cook *et al.*, 1967; Wacker and Parisi, 1968; Seller *et al.*, 1970a,b). Although Rona *et al.* (1963) could not protect against the myocardial necrosis (produced by massive doses of isoproterenol) with estrogens, female rats are more resistant than are males to this form of cardiac damage, an effect that Rona *et al.* (1963) attributed to the slower rate of growth of the females. Possibly, the protective effect of estrogens in these experimental models might be mediated by increased uptake of magnesium by the myocardium, as well as by other tissues, in response to estrogen. Additional evidence that estrogen, or other female sex hormones, might be protective against several forms of cardiovascular lesions derives from study of the influence of pregnancy on experi-

TABLE 5-7A. Sex Difference: Estrogen Effect on Digoxin Toxicity in Dogs[a]

Subjects	Arrhythmia (av. minutes to onset)	Fate
7 males	13.6	Fibrillation (7) { 1 survived on treatment; 1 terminated; 5 died
14 females (castrate)	14.3	Fibrillation and death in all
13 females (castrate + estrogen)	31.7	All survived
4 females (anestrus)	26.0	All survived
3 females (estrus)	71.6	All survived

[a] Adapted from EH Grinnel and PW Smith: *Proc Soc Exp Biol Med* 94:524–527, 1957.

TABLE 5-7B. Protection Against Cardiovascular Lesions by Estrogen

	Abnormality	Produced by	Estrogen protection[a]	Investigator(s)
Dogs	Arrhythmia	Digoxin	2 mg/day	Grinnell and Smith (1957)
Rats	Cardiomyopathy	PO_4 + corticosteroid	10 mg/day	Selye (1970a)
Rats	Cardiomyopathy	Digitalis	10 mg/day	Selye (1970a)
Rats	Cardiomyopathy	Dihydrotachysterol	2 mg/day	Selye (1970a)
Rats	Cardiomyopathy	Isoproterenol (80 mg/kg)	No protection	Rona *et al.* (1963)

[a] Magnesium administration also protects.

mental models. Advanced pregnancy in rats has protected against: (1) dihydrotachysterol-induced arteriosclerosis (Selye, 1957); (2) the cardiovascular necrosis and calcification and calcification of vitamin D excess (Potvliege, 1962); phosphate + corticoid-induced cardiomyopathy (Selye, 1958a); and hyperparathyroid myocardial necrosis (Lehr and Krukowski, 1961a,b; Krukowski, 1961, 1963; Lehr, 1965b). Pregnant dogs are more resistant than are nonpregnant females to necrotizing arteritis produced by a high-fat diet and renal insufficiency (Holman and Jones, 1953).

5.1.4.3. Magnesium, Estrogen, and Thrombotic Events

It is possible that the paradoxical effects of estrogen on diseases of the cardiovascular system relate partially to its effects on magnesium distribution. It has been shown that serum magnesium falls with the cyclic increase in estrogen secretion (Dahl, 1950; Nida and Broja, 1957; Goldsmith, 1963; Goldsmith *et al.*, 1970; Goldsmith, 1971). The use of estrogen-containing oral contraceptives has been shown to reduce the serum levels of magnesium (in users versus nonusers) by 16% (Goldsmith *et al.*, 1966), 28% (DeJorge *et al.*, 1967), and by 27% and 33% (Goldsmith, 1971). Evaluation of different contraceptives suggests that it is the estrogen moiety that is responsible for the decrease in serum magnesium (Goldsmith and Goldsmith,

1966; Goldsmith *et al.*, 1970; Goldsmith and Johnston, 1976/1980), although there are conflicting findings. Since rats given estrogen showed decreased serum magnesium levels, wtihout increased urinary magnesium output, and since the bone-magnesium increased, Goldsmith and Baumberger (1967) proposed that a shift of magnesium to the tissues was responsible for the estrogen-induced fall in serum magnesium. Indirect support for the importance of the estrogen component of contraceptives in lowering serum magnesium comes from the report that progestogens increase rather than decrease serum magnesium (Dale and Simpson, 1972). Yet, norethisterone and mestranol, alone or combined, have been shown to increase magnesium levels in bone, muscle, and intestinal wall tissues (Gozan and Charnot, 1973; Charnot *et al.*, 1974). Despite the increase in tissue levels of rats on mestranol, their serum magnesium levels did not fall; norethisterone, however, produced a 30% drop in serum magnesium (Gozan and Charnot, 1973). The picture is further confused by the studies showing no effect of several oral contraceptives on serum magnesium (N. Hahn *et al.*, 1972) or on magnesium levels of plasma, erythrocytes, and platelets (Thin, 1971). Data on decreased serum magnesium levels during pregnancy are discussed elsewhere in this volume, as possibly reflecting a true magnesium deficit rather than a hemodilution or estrogen-induced effect. Wallach (1976/1980) has considered the findings relating to the effect of estrogen on magnesium and has commented that circumstantial evidence from studies of interrelations of estrogen, calcium, and magnesium on thymic cell proliferation (Morgan and Perris, 1974) suggests that estrogen may favor cellular transport of magnesium.

Although there is no uniform agreement that estrogens lower serum magnesium levels, most of the evidence points in that direction. Thus, the still controversial evidence that low magnesium levels can contribute to coagulopathy deserves consideration as a possible factor in estrogen-induced thrombotic disorders. Durlach (1967a,b,c) first described severe thromboembolic disease in a young woman with latent tetany of magnesium deficiency. Her disorder was associated with increased ADP-induced platelet aggregation. Additional instances have since been reported in women with latent tetany of magnesium deficiency (DuPont *et al.*, 1969; Durlach, 1970; Boudet *et al.*, 1972; Erödi, 1973; Debrand, 1974; Maurat *et al.*, 1974; Seelig *et al.*, 1976/1980). Durlach (1970) has also shown that estrogen therapy gives rise to both functional platelet alterations and to signs of magnesium deficiency, which regress on administration of oral magnesium in moderate dosage. Vajna (1971/1973) has claimed that administration of magnesium to women on oral contraceptives significantly reduces the risk of coagulopathy.

Elin (1976/1980) and Durlach (1976/1980) have reviewed the *in vitro* evidence that magnesium plays a role (predominantly inhibitory) in the coagulation process. However, as Durlach (1976/1980) stresses, most of the *in vitro* studies showing that magnesium can inhibit coagulation factors—prothrombin, thrombin, and Factors V, VII, and IX—and can increase fibrinolysis, have been based on studies with high magnesium concentrations. They are thus not directly relevant to consideration of the effects of low or marginally low serum magnesium levels on the tendency toward intravascular coagulation. A few experimental magnesium-deficiency studies may shed light on the clinical coagulopathy of magnesium deficiency or on that accompanying use of agents (such as estrogens) that lower serum magnesium levels.

Stevenson's and Yoder's (1970) magnesium-deficient animals had significantly shorter thrombin clotting time and greater ADP breakdown than did the normal group ($p \leq 0.001$). The partial thromboplastin time was also significantly reduced in magnesium-deficient calves ($p \leq 0.05$). Stachura (1971) observed hypercoagulation with shortened thromboplastin time in magnesium-deficient rats. Magnesium-deficient calves had insignificantly increased ADP-platelet aggregation ($p \leq 0.05$) but magnesium-deficient rats had more ADP-platelet aggregation ($p \leq 0.05$) than did normal rats (Stevenson and Yoder, 1970). Since magnesium-deficient rats commonly develop hypercalcemia (Larvor and Durlach, 1971a; Seelig and Haddy, 1976/1980),the species difference in ADP platelet response to magnesium deficiency might reflect the presumed difference in the Mg/Ca ratio in the rats versus the calves (data on calcium levels were not provided).

Hypercoagulability, produced by feeding rats a thrombogenic diet containing cholesterol, vitamins D_2 and D_3, and thiouracil, as well as large amounts of butter, was counteracted by oral magnesium chloride (Szelenyi *et al.*, 1967) (Fig. 5.2). Dogs acutely loaded with butter showed markedly increased blood coagulability three hours later. Magnesium, given intravenously at the time of intragastric butter administration, prevented the decreased coagulation time and the increased prothrombin consumption (Szelenyi *et al.*, 1967) (Fig. 5-3).

Clinical studies of the effects of magnesium administration to patients with cardiovascular disease and hyperlipidemia have been considered. Relevant to this section are the reports that parenteral magnesium therapy reduced plasmin inhibition (R. Parsons, 1958). Other studies suggest that magnesium therapy accelerates fibrinolysis (Hackethal, 1949; Zahnert and Oloffs, 1960). Further clinical investigation of effects of magnesium on blood coagulation and clot lysis is required.

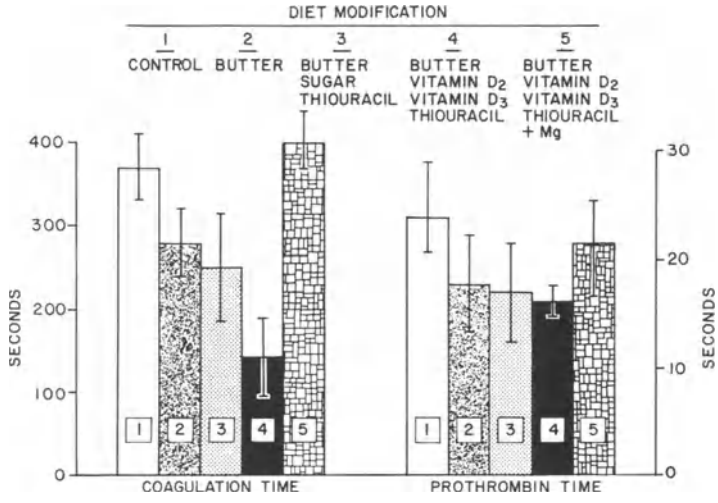

FIGURE 5-2. Effect of magnesium on coagulation times of rats on thrombogenic or cardiopathic diets. (Adapted from Szelenyi *et al.*, 1967, 1971.)

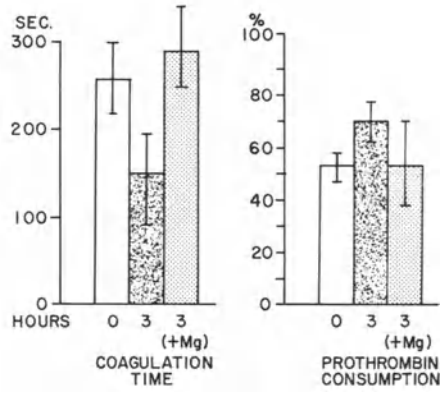

FIGURE 5-3. Effect on canine clotting functions of acute butter load without and with magnesium, i.v. (Adapted from Szelenyi *et al.*, 1967.)

Elin (1976/1980) has reviewed *in vitro* evidence that magnesium affects platelet aggregation and release. Its inhibitory effects on platelet aggregation have been with high concentrations (Born and Cross, 1964); the calcium/magnesium ratio is important at low concentrations (Herrman *et al.*, 1970). Platelet release is calcium dependent (Sneddon and Williams, 1973); increasing concentrations of magnesium are inhibitory (Sneddon, 1972).

Whether these findings are relevant to the increased blood coagulability and platelet adhesiveness of patients with myocardial infarctions remains to be resolved. Hughes and Tonks (1965) reported significantly decreased serum magnesium levels and increased platelet aggregability in infarct patients, as compared with matched controls, a finding reported also by Prakash *et al.* (1971/1973). Chadda *et al.* (1976/1980) have also reported decreased serum magnesium in such patients. However, Murnaghan *et al.* (1969) reported elevated serum magnesium levels and Khan *et al.* (1974) normal levels, the latter in association with highly significantly increased platelet adhesiveness. In view of the known stress and anoxia-induced magnesium egress from the tissues, with initially increased serum magnesium, followed later by decreased serum magnesium levels, longitudinal studies of infarction patients must be done with meticulous attention paid to the time lapse after the ischemic event; and to the degree of decompensation-hypoxia.

6
Is Clinical Arteriosclerosis a Manifestation of Absolute or Conditioned Magnesium Deficiency?

6.1. The Arterial Wall and Arteriosclerosis

The major emphasis of the preceding sections on magnesium–lipid interrelationships and on estrogen–lipid/coagulation–lipid interrelationships is predominantly on blood constituents, as they influence the development of atherosclerosis.

The likelihood that metabolic and structural alterations in arterial walls may predispose to their increased accumulation of lipids has also been investigated. The need to consider, not only alterations in the constituents of blood but also in the status of the containing vessels, was commented upon by Duff and McMillan (1951) in their review of changing concepts of the pathogenesis of arteriosclerosis. They observed that the view that chemical and physicochemical aberrations of the serum lipids and lipoproteins are fundamental to the pathogenesis of arteriosclerosis had become so popular that " . . . the casual reader of recent literature might wonder whether some authors conceive of an atherosclerosis so independent of the substrate of the vessel wall, that it may occur in the absence of the blood vessels themselves."

6.1.1. Mucopolysaccharides and Elastica in Arteriosclerotic Arteries

Specific alterations in the mucopolysaccharides have been observed in the ground substance of arteriosclerotic arteries obtained from human material. Increased metachromasia, due to elevation in acid mucopolysaccharides, occurs in arteries from human material prior to lipid infiltration in aging and in arteriosclerosis

(Faber, 1949; Moon and Rinehart, 1952; Moon, 1959; Gresham *et al.*, 1962). It has been suggested that it develops in areas characterized by prior degeneration of the elastica and predisposes to infiltration by lipids (Moon and Rinehart, 1952; Taylor, 1953; Moon, 1957, 1959). On the other hand, it has been postulated that lipids in arterial lesions derive from the degenerated elastic fibers and that the elevation in mucopolysaccharide reflects a healing process (Zugibe and Brown, 1960; Zugibe, 1963).

*6.1.2. Pathology of Infantile Arteriosclerosis**

Intimal, subintimal, and medial arterial lesions, usually of the small- and medium-sized arteries, such as have been described in infants who died suddenly or after protracted congenital cardiac disease, are characterized by elastica degenerative processes, mucopolysaccharide or calcium deposition, and proliferative or fibrotic intimal and medial changes. Lipid droplets are often also seen, but the fat deposition does not become atheromatous until later in infancy and childhood. The very early infantile arterial lesions resemble those of magnesium deficiency in animals with otherwise balanced diets, i.e., "pure" magnesium deficiency. Suddenly fatal arterial lesions of infants have usually been coronary (associated with perivascular myocardial microfocal necrosis, or more rarely with gross infarctions). However, most of the infants with coronary lesions also had arteriosclerosis of other viscera and occasionally had generalized arteriosclerosis. Whether earlier arterial lesions exist in infants who develop "adult-onset" atherosclerosis or in infants born to parents with early cardiovascular disease is difficult to ascertain.

Even among infants identified as having had cardiovascular disease pre- or postmortem, the degree and location of arterial damage are often not specified. Among the 157 separately cited cases of infants born dead or dying within the first month of life with cardiac lesions, 30 had coronary arteriosclerosis described and 14 had visceral or generalized arteriosclerosis described. Although not mentioned, coronary arterial lesions are probable in at least 80 more who had myocardial lesions ranging from necrosis with and without calcification to fibrosis. Only 5 of the 80 with endocardial fibroelastosis had coronary arterial lesions mentioned. Among the 253 infants tabulated as having died of cardiovascular disease from 1 month to 2½ years of age, 85 were described as having coronary arteriosclerosis, with or without involvement of other arteries. Myocardial lesions suggestive of ischemic heart disease were described in an additional 74 infants, whose coronary arterial status was not described. Almost half of the 110 infants with endocardial fibroelastosis did not have coronary arterial or myocardial lesions described. Among those whose arterial lesions were described, a third of those up to 1 month of life had intimomedial proliferation and almost as many had thrombosis noted. About half of the infants of 1 month to 2½ years of age, whose arteries were described, had intimomedial proliferation, but only a tenth had thromboses. It is not possible to ascertain the incidence of intimomedial proliferation from surveys of autopsy material, for some include intimal sites of proliferation, "cushions" as

* See Appendix Tables A-5A,B and A-6A,B.

precursors of atheromata (Dock, 1946; Fangman and Hellwig, 1947), and others specifically exclude them as normal variants (Schornagel, 1956; Oppenheimer and Esterly, 1967).

With one exception, the 19 children whose arteries showed degenerative or calcific changes were no more than 4 days old at death. This might be supportive of Gruenwald's (1949) conclusion that perinatal hypoxia can cause arterial necrosis, based on his finding such lesions in as many as 9.5% of infants autopsied after stillbirth to 3 days of life. There were fewer instances of intimomedial degenerative changes in the older infants, but more instances of calcification. Three cases of lipid deposition in the arteries were noted in the individual case reports of infants up to one month of age; 6 were noted in the group up to 2½ years.

Few patients with supra- or subvalvular aortic stenosis or with cardiofacial peculiarities are cited; most survived beyond the 2½-year limit selected. That these children probably developed their abnormality either *in utero* or in the first 2 years of life seems likely.

6.1.3. Incidence of Infantile Coronary Arteriosclerosis

This is a disease, the incidence of which is impossible to estimate. As a result of the effort to classify infants with histopathologically identical lesions as suffering from different diseases, depending on coexisting anomalies or demonstration of conditions that predispose to metastatic calcification, there is not uniformity of reporting. Further complicating the determination of the incidence of infantile coronary arteriosclerosis is the lack of agreement as to what the infantile arteriosclerotic lesion is. In "idiopathic" infantile arteriosclerosis, intimal thickening and elastica degeneration are recognized as the typical findings, but focal intimal proliferative, termed "cushions" (usually with fibromuscular disorganization of the media), which are found more than twice as often as are atheromas, are not uniformly considered pathological. When only atheromatous lesions are considered evidence of arterial disease, neonatal focal myocardial necrosis has been reported in the absence of lesions of the main coronary arteries. Rarely are the intramyocardial arteries examined. Thus, coronary occlusion or significant coronary disease is less frequently reported than is that of the myocardium or endocardium. Nonetheless, an attempt to select, from the pathology surveys, cases designated by the age groups selected here, and that exclude major anomalies (other than atresia of the great vessels), suggests about 500 in which hypoxia of the heart might have been involved in infants up to one month of age, and over 2000 in those from 1 month to 2½ years of age.

In the case of endocardial fibroelastosis (EFE), myocardial ischemia has been repeatedly implicated. J. M. Craig (1949), who presented 43 cases, noted that microscopic myocardial necrosis and fibrosis was common. He suggested intramural coronary disease *in utero* as a contributory factor. F.R. Johnson (1952) suggested that intrauterine anoxia might be contributory to the EFE seen in malformed hearts; Moller *et al.* (1966) noted that infarcts of the papillary muscles are not infrequently found in infants with EFE. Since the subendocardial myocardium obtains oxygen from the blood in the heart chambers, conditions that interfere with blood outflow,

that lead to stagnation, can lead to hypoxic subendocardial and endocardial damage and thickening. In fact, outflow obstruction is the most common anatomic disorder associated with EFE (Moller *et al.*, 1964; Bryan and Oppenheimer, 1969).

A survey of necropsy material in a major medical center showed that myocardial infarction is not rare in infants, even occurring *in utero* (Franciosi and Blanc, 1968). In infants with congenital heart disease, the infarcts were limited to papillary muscles (which are supplied by the small end-arterial branches of the coronaries), and to microscopic lesions of the subendocardial ventricular myocardium that were adjacent to perivascular and interstitial fibroses. Although none was associated with occlusive arterial disease, grade 1 to 4 coronary lesions were found frequently. Grade 1 was characterized by frayed intimal elastica lamina; grade 2 additionally had slight focal intimal fibrosis; grade 3 had intimal cushions in addition; grade 4 had diffuse elastica fraying and diffuse intimal thickening equaling the thickness of the media. The frequency of the infantile myocardial infarcts was 80% among those with anomalous venous return, 89% in those with pulmonary valvular stenosis, and 100% in those with aortic valvular stenosis.

The coronaries are often not examined, even among infants who die during the perinatal period and are autopsied. This is particularly so in the case of the small- and medium-sized arteries, which are most often involved in infantile coronary arteriosclerosis, and which are most likely to be involved in focal and microscopic myocardial necrosis and fibrosis and in fibroelastosis. Blanc *et al.* (1966) pointed out that systematic examination of the small- to medium-sized coronaries of infants has disclosed that as many as 12% had arteriosclerosis.

Despite the fact that many of the infants with necropsy evidence of coronary disease had died suddenly, none were recorded as having been reported by medical examiners or coroners (Moran and Becker, 1959). Thus, it seems likely that many of the instances of this disease are not recognized. Supporting the contention that many cases might be missed are the studies of autopsy material that include examination of the large coronaries of infants. In a study of the proximal segments of the main coronaries of 105 individuals who died before birth to the early twenties, only the fetuses (24 of 3½–9 months gestation) were free of coronary lesions (Moon, 1957). In that series, two premature infants had ruptured internal elastic membranes but had no other coronary lesions. Most of the 52 infants under two years of age had coronary lesions, the earliest noted being rupture and degeneration of the internal elastic membrane. Some also had fibroblastic proliferation with deposition of mucopolysaccharides and proliferation of endothelial cells overlying these areas. Infants several months old had progression of the intimal lesions as compared with newborn infants, the intimal thickening being very pronounced at three or four months of age. The intima was commonly thicker than the media. Serial sections of the left anterior descending coronaries of 88 infants, from stillborn to one year of age, also showed that intimal thickening increased with the infants' age (Schornagal, 1956). Grading the lesions I (endothelium on regular or split elastica interna) to III (thick intima), about 40% of the males had grades II and III lesions at less than one day to one month, and 24% and 37% of the females at less than one day and up to one month, respectively. Infant boys and girls of one month to one year had grades II and III coronary lesions in 91.3% and 87.5%, respectively. That the earli-

est coronary lesions in the youngest infants is elastica degeneration, often without overlying intimal thickening, was attested to by Levene (1956), Gillman (1959), and Kaunitz (1961). The intimal hyperplasia, usually in the areas with elastica damage, was pointed out in the early studies of Dock (1946) and Fangman and Hellwig (1947), both of whom stressed the preponderance of intimal thickening in male neonates. Because these neonatal coronary lesions are so common, there is controversy as to whether they are the earliest arteriosclerotic lesions or merely adaptive phenomena (Review: Neufeld and Vlodaver, 1971). This group confirmed the greater degree of elastica degeneration and overlying intimal fibroblastic proliferation, as well as muscle degeneration in the media, in male than in female Jewish neonates of European derivation (Ashkenazim) but found far less sex difference in intimal thickening among Yemenite (Mideastern Jewish) and Bedouin infants (Fig. 6-1) (Neufeld and Vlodaver, 1968, 1971). Histologic examination of right and left coronaries from 211 consecutive hearts from fetuses, infants, and children up to ten years of age showed significantly higher intima/musculoelastica ratios among the Ashkenazi males than among Yemenite or Bedouin males (Neufeld and Vlodaver, 1968; Vlodaver *et al.*, 1969). Since the infants with the greatest degree of intimal damage (Fig. 6-2) were from the ethnic group with the highest rate of adult ischemic heart disease, it was considered likely that the early coronary lesions were indeed the precursors of the later coronary atherosclerotic lesions (Neufeld and Vlodaver, 1971; Neufeld, 1974).

Although coronary and myocardial lesions were most often the causative factors in the terminal event, most of the babies with coronary disease also had arteriosclerosis of other arteries, generally (in order of frequency) of the kidneys, adrenal glands, pancreas, spleen, lung, mesentery, and thyroid (Review: Moran and Becker, 1959).

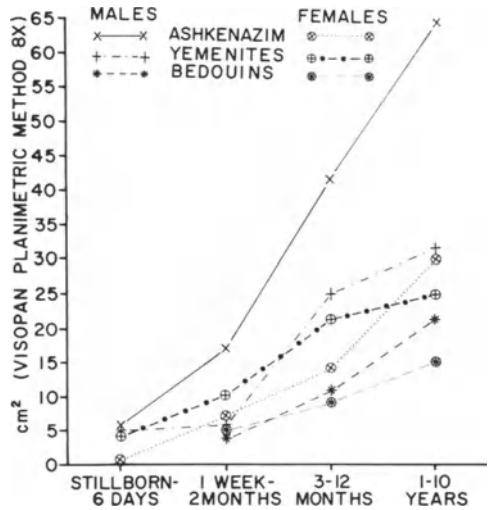

FIGURE 6-1. Mean values of measurements of intima and musculoelastic layer in coronary arteries in three ethnic groups. (Adapted from Neufeld and Vlodaver, 1971.)

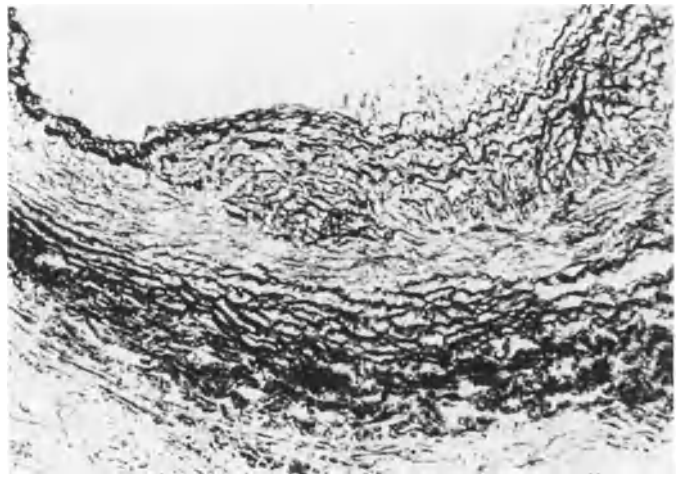

FIGURE 6-2. Pronounced changes in the internal elastica of the left coronary artery of a 2-month-old Ashkenazy male. Elastic tissue stain: van Gieson, × 70. (From Z Vladaver *et al.: Circulation* 39:541–550,1969.)

6.2. *Factors Suggesting Magnesium Deficiency in Infantile Cardiovascular Disease*

The type of coronary arteriosclerosis, particularly of the small-to-medium coronary arteries, and the perivascular focal myocardial necrosis (that are seen in infancy) strongly resemble the coronary and myocardial lesions produced in animals on magnesium-deficient diets (Seelig and Haddy, 1976/1980). Most of the magnesium-deficient animals with cardiovascular lesions were immature. There have been comparable changes reported in herbivores however, usually during early lactation, occurring in herds grazing on magnesium-poor lands, on pasturage with factors interfering with availability of magnesium, and not infrequently in herds with a high incidence of eclampsia (Arnold and Fincham, 1950; Lynd *et al.*, 1965; Willers *et al.*, 1965; review: Seelig and Bunce, 1972). Data on abnormalities during pregnancy or delivery are not frequently given in papers on infantile cardiovascular disease. Some information was given in a third of the tabulated infants who died under one month of age and in less than a third of those with the disease reported in infants from one month to two and a half years of age (Appendix Table A-6A). Abnormal or frequent pregnancies, long or complicated deliveries, immaturity during gestation, multiple births, and maternal diabetes mellitus—all conditions that have been associated with low levels of magnesium—and placental insufficiency or premature separation of the placenta are conditions associated with prenatal hypoxia and malnutrition. Several of these factors were cited in eight of 29 infants dying with myocardial lesions, who had fetal distress recorded (Oppenheimer and Esterly, 1967). Such factors plus hydramnios or RH incompatability were reported in 63 of the 157 of those under one month of age (Appendix Table A-5A), but in only 38 of the 251 infants over one month to two and a half years old (Appendix Table A-6A), few of whom had maternal histories cited. There were several

instances in which there had been previous unsuccessful pregnancies, or in which siblings or close relatives had died similarly. Thus, it seems that metabolic disorders or gestational stress (especially in instances of maternal immaturity, or frequent or multiple pregnancies) might have played roles in absolute or conditioned magnesium deficiency. Unfortunately, magnesium levels were almost never recorded in the propositus or mother, leaving speculative the supposition that magnesium deficiency might have been contributory in the cited cases. An exception is the infant, reported by Vainsel *et al.* (1970), who had hypomagnesemic hypocalcemia and whose refractoriness to vitamin D and calcium therapy appeared to be familial. He and three male siblings (out of six) had had convulsive seizures. One died at six weeks; the described infant died at three months and was found to have focal myocardial necrosis and coronary calcinosis. Since he was the ninth infant in his family, both a metabolic and multiparity-induced hypomagnesemia might have participated in his severe hypomagnesemia (0.4–0.65 mEq/liter), the magnesium deficiency having been detected only a few days before death (Vainsel *et al.*, 1970). Until prospective and retrospective magnesium data are obtained from affected infants and their mothers, from subsequent pregnancies and infants, and from near relatives, the validity of the premise that magnesium deficiency is contributory to infantile ateriosclerosis and its complications remains untested.

The medial necrosis of the coronaries seen in large infants with birth asphyxia (Gruenwald, 1949) might also be related to loss of tissue magnesium. Perhaps sufficient magnesium can leave the tissues of the coronary arteries and the heart to cause necrosis or arrhythmia or both. The intimal and medial loss of functional myocardial magnesium (Review: Seelig, 1972) might participate in the cardiac lesions of infantile cardiovascular disease.

Perhaps contributing to infantile coronary arterial lesions and microfocal myocardial necrosis (that either results in immediate death or sets the stage for cardiac death in the later months or years) is neonatal hypoparathyroidism. Lehr and his colleagues (Lehr, 1965, 1966; Lehr *et al.*, 1966) have shown that parathyroidectomized rats, particularly when they are phosphate loaded, develop lesions of the small coronary arteries and perivascular microfocal myocardial necrosis. The high phosphate content of cows' milk, fed to infants during the neonatal period, especially when their parathyroid hormone secretion is often subnormal, and the hyperplasia of infants' coronaries might also be related to episodes of hypoxia, conceivably such as are experienced by infants that suffer from periods of sleep apnea (as in the SIDS). The production of severe arteriosclerosis, predominantly of the arterial connective tissues, by exposure of rabbits to short periods of hypoxia daily for two weeks (Helin *et al.*, 1969; Garbarsch *et al.*, 1969) would seem to support that supposition. Not noted in Gruenwald's (1949) study of large infants whose medial necrosis was attributed to perinatal anoxia was whether any had been born to diabetic mothers. Infants of diabetic mothers not only tend to be large but have also been found to have a high incidence of hypomagnesemia.

In the infants past the neonatal period, the use of cows' milk formulas that not only provide a substantial phosphate load, but that also provide vitamin D additional to that generally prescribed by the physician, can also contribute to magnesium deficiency. The generalized arteriosclerosis, valvular disease, and fibroelastosis of babies that have received excessive vitamin D or that are hyperreactive to

it have been reviewed (Seelig, 1969b, 1978; Seelig and Haddy, 1976/1980; Seelig and Mazlen, 1977). Regarding its effects during pregnancy, experimental hypervitaminosis D has been implicated in placental abnormalities, such as those that contribute to fetal malnutrition, anoxia, and possibly to eclampsia. It is well to remember, thus, that vitamin D excess causes magnesium loss that might well be implicated in infantile cardiovascular disease (Seelig and Haddy, 1976/1980).

6.2.1. Experimental Arteriosclerosis of Magnesium Deficiency

6.2.1.1. Arterial Damage Caused by "Pure" Magnesium Deficiency

Since most of the studies of the pathogenesis of atherosclerosis have focused on fat, and most studies of magnesium deficiency were with animals (usually rats) whose control and experimental diets were also high in calcium, phosphate, and often vitamin D (Reviews: Larvor and Durlach, 1971b; Seelig and Haddy, 1976/1980), there are few experimental studies of the vascular changes caused by magnesium deficiency alone (Fig. 6-3). Lowenhaupt *et al.* (1950) reported that young rats kept on a normal diet, except for magnesium deficiency, developed myocardial lesions (within two weeks) around the small coronary radicals of precapillary and capillary size. Other magnesium-deficiency studies, that elicited focal myocardial infiltration, necrosis, and scarring (Mishra, 1960a; Mishra and Herman, 1960; Seta *et al.*, 1965) are suggestive of damage to the small intramyocardial coronaries. Heggtveit (1965c) reported edema of the small coronary arteries in Mg-deficient rats. Hungerford and Bernick (1976/1980) have provided details of the nature of the coronary arterial damage produced by magnesium deficiency in rats: intimal thickening with extracellular edema, thinning of the internal elastic membrane with disruption, and disorientation and hyperplasia of medial muscle cells. Some of the arteries had densely aggregated pyknotic cells in their enlarged tunica media, with narrowed lumina. This group confirmed the inflammatory changes of the perivascular myocardium, reported more than 25 years earlier by Lowenhaupt *et al.* (1950). Dogs on otherwise balanced magnesium-deficient diets had pyknotic intimal cells in small coronary arteries and arterioles, 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). Intimal and medial calcification were described in magnesium-deficient dogs, despite

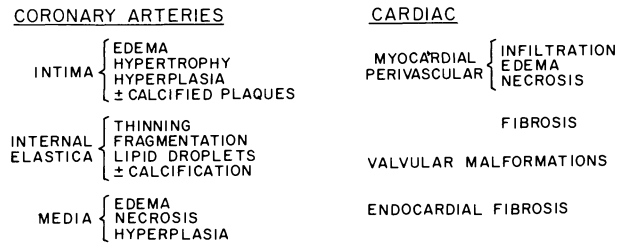

FIGURE 6-3. Coronary arterial and cardiac lesions of "pure" magnesium deficiency in rats, dogs, and ruminants. (From Seelig and Haddy, 1976/1980.)

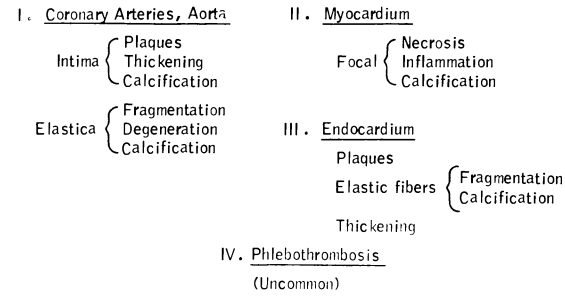

FIGURE 6-4. Intensification of magnesium-deficiency cardiovascular lesions by high intakes of vitamin D and calcium. High Ca interferes with intestinal Mg absorption and renal tubular Mg reabsorption. High vitamin D increases net Mg loss in favor of Ca retention (both lead to an increase in Mg requirements and intensify Mg deficiency). (From Seelig and Haddy, 1976/1980.)

decreased serum calcium levels (Syllm-Rapoport and Strassburger, 1958; Unglaub *et al.*, 1959; Bunce *et al.*, 1962b; Featherston *et al.*, 1963; Morris *et al.*, 1963; Wener *et al.*, 1964). As in the magnesium-deficient rats, which had perivascular myocardial necrosis and edema (*supra vide*), magnesium-deficient dogs had comparable myocardial lesions (Unglaub *et al.*, 1959; Wener *et al.*, 1964). Large myocardial infarcts were seen in severely magnesium-deficient dogs (Morris *et al.*, 1963).

The histologic arterial changes of magnesium deficiency were first characterized in cows, on spring forage on magnesium-poor soil, or where other factors interfered with the availability of magnesium (Arnold and Fincham, 1950). These observations were 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. Medical calcification and calcific intimal plaques were also described, as were valvular malformations and myocardial infarcts (Willers *et al.*, 1965). The syndrome, leading to these cardiovascular lesions, was seen predominantly in lactating cows in areas where "grass tetany" or convulsions of magnesium 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, 1966a,b).

6.2.1.2. Arterial Damage of Magnesium Deficiency, Intensified by High Calcium and Vitamin D Intakes (Fig. 6-4)

High dietary calcium/magnesium dietary ratios have uniformly increased the susceptibility to the symptoms and signs of magnesium deficiency. It is important to remember that high intakes of calcium interfere with magnesium intestinal absorption and increase its renal excretion, and that high intakes of vitamin D also favor calcium retention over that of magnesium (Reviews: Seelig, 1964, 1971).

Cardiovascular changes, similar to those seen in "pure" magnesium deficiency, developed in rats fed 400–650 times as much calcium as magnesium (versus 40/1 in controls, which is also a much higher than normal Ca/Mg ratio). There were small inflammatory and necrotic myocardial lesions (suggestive of disease of the small coronary arteries) with increased tissue calcium and sodium, but no significant change in serum calcium, and low tissue and serum magnesiun and potassium (Mishra, 1960a; Ko *et al.*, 1962). Adding sufficient magnesium to lower the Ca/Mg ratio to 3/1 prevented the lesions (Mishra, 1960a). In a study designed to show how much magnesium is necessary to prevent macroscopically manifest intimal calcific plaques in dogs on Ca/Mg intakes of 33–50/1, Bunce *et al.* (1962a) found a little more than a twofold increase in grossly visible aortic intimal lesions in dogs receiving 0.6% of calcium (Ca/Mg = 33/1). Most of the dogs on high calcium/low magnesium intakes had intimal plaques.

Since vitamin D normally increases serum calcium levels and increases magnesium requirements, it is of interest that magnesium-deficient dogs on normal calcium intakes showed minimal coronary arterial calcification unless they were given vitamin D or an intravenous calcium load (Syllm-Rapoport and Strassburger, 1968; 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 D excess causes arteriosclerosis has been known even longer (Kreitmair and Moll, 1928). Like the arterial lesions of magnesium deficiency, those of experimental hypervitaminosis D (Gillman and Gilbert, 1956) involve medial and elastica degeneration and calcification (Review: 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 magnesium supplementation (Sos *et al.*, 1960; Rigo, 1965; Rigo *et al.*, 1965a; Sos, 1965).

When calves were fed low-magnesium diets that were usually comprised of whole milk or a comparable synthetic diet (both supplemented with vitamin D) for prolonged periods, they developed neuromuscular signs of magnesium deficiency and endocardial and intimal plaques, and fragmentation, degeneration, and calcification of the elastic fibers of both endocardium and arteries, and phlebothrombosis and focal myocardial necrosis (Moore *et al.*, 1936, 1938; Blaxter *et al.*, 1954). The magnesium-deficiency syndrome was prevented by magnesium supplementation: 30–40 mg/kg/day (Huffman *et al.*, 1930; Duncan *et al.*, 1935; Moore *et al.*, 1936, 1938; Blaxter *et al.*, 1954). Like human infants, despite these calves' high calcium intakes, their serum calcium remained normal or slightly low. In addition to the endocardial and intimal calcification, calves on a whole-milk diet developed high serum cholesterol levels (J. W. Thomas, 1959).

6.2.1.3. Arterial Damage of Magnesium Deficiency Intensified by High Fat Intakes (Table 6-1)

Studies of the influence of magnesium deficiency and its repletion on the development of atherosclerosis in rats (fed different combinations of saturated or unsat-

TABLE 6-1. Cardiovascular Lesions of High-Fat, Low-Magnesium Diets[a]

Arteries		Myocardium
Intimal fibroblastic thickening		Ischemia Necrosis Fibrosis (microfocal; massive)
Intimal fat streaks		
Subintimal, Medial	degeneration	
Endothelial	plaques, atheromata	
Elastica	fragmentation, thickening	

[a] Lesions intensified by magnesium deficiency and protected against by magnesium supplements.

urated fat diets with and without added cholesterol and cholic acid and calcium) (pages 148–152) have shown dissociation between serum and cardiovascular lipids. It is noteworthy that increased magnesium intakes of animals on atherogenic, hyperlipidemic diets decreased arterial and myocardial lipid deposition without lowering the elevated serum lipids; the magnesium even raised the serum lipids somewhat (Vitale *et al.*, 1957d; 1959; Nakamura *et al.*, 1960). In contrast, high calcium intakes lowered the serum lipids but raised the arterial lipids (Vitale *et al.*, 1957c; 1959; Hellerstein *et al.*, 1957, 1960; Nakamura *et al.*, 1960). Long-term administration of magnesium to rats on atherogenic diets, which only gradually lowered serum lipids to a minor degree, resulted in more rapid and significantly reduced arterial lipid deposition (Nakamura *et al.*, 1960, 1966). The rats on the low-magnesium, high-fat diets were the only high-fat-fed rats to develop fat deposition in heart valves and plaque formation in the aorta (Nakamura *et al.*, 1966). In this series of experiments, subintimal and medial degeneration and calcification of the elastica, as well as intimal atheromata, developed only in the rats that were magnesium deficient as well as fat loaded. Calcification of the media of pulmonary artery and of the myocardium (some with interstitial inflammatory infiltration) were also noted in magnesium-deficient, fat-loaded rats. In a further study to explore the mechanism of the intensification of atheroma formation by magnesium deficiency of rabbits on an atherogenic diet, Hirano (1966) measured the uptake of radioisotope ^{14}C-tagged cholesterol by the heart, aorta, and other viscera. Rabbits fed the magnesium-deficient atherogenic diet showed increased radioactivity in the aorta, as compared with controls. Even magnesium-deficient rabbits on low-cholesterol intakes had increased fat deposition in the aortas, but to a lesser degree. Despite the increase in aorta cholesterol in magnesium-deficient rabbits, the serum cholesterol level was not significantly altered.

Nakamura *et al.* (1965) found that rabbits that had developed atherosclerosis required substantial amounts of magnesium added to their diets to exert a notable effect on atherogenesis. More than 950 mg/100 g of diet was necessary to affect serum and tissue lipids. The authors commented that aortic lipid deposition is sig-

nificantly enhanced by magnesium deficiency; high magnesium intake merely slows the process. The elevated intimal plaques, fragmented and calcified elastica, and mural thrombi that were reported in the magnesium-deficient rabbits, were not seen in the matched cholesterol-loaded, magnesium-supplemented rabbits; they showed no calcified lesions and less foam cells in the subintimal layer of the aorta (Nakamura *et al.*, 1965). Narrowing of coronary arteries was noted in all of the cholesterol-loaded rabbits, but to a somewhat lesser degree in the rabbits on high magnesium intakes. Greater involvement of the small coronary arteries is suggested by the microscopic foci of myocardial necrosis in half the rabbits on magnesium-deficient, high-cholesterol diets, but in none of those that were magnesium supplemented. Bunce *et al.* (1962a) showed that increasing the magnesium intake, sufficiently to prevent intimal lesions in dogs on a high saturated fat diet, actually increased their serum cholesterol levels, whereas the dogs on the highest Ca/Mg ratio had lower serum cholesterol (270%) and more intimal lesions. Dogs on a magnesium-free, corn-oil-rich, low-calcium diet had intimal thickening and plaques with narrowed coronary 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.

These findings raise the question as to whether seeking to correlate serum magnesium and cholesterol levels provides meaningful data regarding the influence of magnesium deficiency or therapy on atherosclerosis. Even when high doses of magnesium are given to hypercholesterolemic animals, the changes in serum lipids are less consistent than is the lowering of tissue lipids. The serum levels of cholesterol have been unaffected, or even raised in some of the studies; the β-lipoprotein fraction seems to be influenced somewhat more. Although magnesium deficit intensifies atheromatosis, it takes quite large doses and/or prolonged administration of magnesium to protect against the disease in hyperlipemic animals (Hellerstein *et al.*, 1957; Rigo *et al.*, 1963, 1965a,b; Nakamura *et al.*, 1965, 1966). It seems that neither the serum magnesium nor cholesterol level are illustrative of the tissue levels. Thus, to determine the effect of magnesium on lipids in man, we must investigate the response to effective doses of magnesium. The preliminary clinical trials cited in this chapter are not conclusive. Prolonged trials with more intensive exploration of the leads mentioned here are indicated. The effect of magnesium on high-density lipids needs study.

6.2.1.4. The Cardiovasopathic (CVP) Diet

An experimental diet (Table 6-2) has been devised that causes spontaneous myocardial infarctions (MI) in 80–90% of the animals (rats, dogs, and cocks) fed that diet but kept under otherwise normal conditions (Sos *et al.*, 1960, 1964a,b,c; Sos, 1965; Rigo *et al.*, 1961, 1963a,b, 1965a,b; Rigo, 1971; Gati *et al.*, 1964, 1965; Szelenyi, 1971, 1973; and Review: Seelig and Haddy, 1976/1980). With the exception of low chloride, it possesses the characteristics of diets consumed by many in our affluent society. It is high in fat, cholesterol, vitamin D, sodium, phosphate, and protein; it is low in magnesium, potassium, and chloride. In addition to the massive infarctions, animals on the CVP diet had atherosclerosis, hyperlipidemia, and

TABLE 6-2. Cardiovasopathic Diet (CVP)[a]

Low in	magnesium potassium chloride	High in	saturated fat cholesterol protein vitamin D sodium phosphate
Normal calcium			

Demonstrated in cocks, rats, dogs

Arterial lesions Atherosclerosis Calcification ↓ Lumen; ↑ wall/lumen ratio ↓ Elasticity	Spontaneous myocardial infarcts ↑ Blood coagulability

[a] Adapted from Sos (1965).

the abnormalities (Table 6-3). Without the added cholesterol, animals on the (modified) CVP diet still had high cholesterol levels, but they were half as high as those on the complete CVP diet. The hypertension was unaffected, but the incidence of MI dropped to 60% of the group. Elimination of only vitamin D did not lower the blood cholesterol, but the animals had only slight hypertension, and fewer (40%) developed MI. Halving the protein content of the CVP diet (to a normal intake) resulted in a slight increase in serum cholesterol, no change in the hypertensive level, but resulted in about half the MI incidence (40%) of the CVP animals. Providing a normal salt mixture lowered the cholesterol somewhat but not the hypertension. It lowered the incidence of infarction to 13%. Increasing the dietary intake of magnesium chloride 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, 1971). The increased magnesium 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 ⅓ each, and adding thiouracil, marked hypercoagulability was produced. Fivefold increased magnesium intake restored the coagulation and prothrombin times to normal (Szelenyi, 1971, 1973).

TABLE 6-3. Serum Cholesterol, Blood Pressure, and Incidence of Infarcts (Effects of Modifying CVP Diet)

Diet	Serum cholesterol	Blood pressure	Incidence of MI
Control	94	112	0
CVP	↑ 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%

TABLE 6-4. Serum and Myocardial Electrolytes of CVP and Control Diets

Diet	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	2.0	6.6	5.0	134	11.7	42	5.5	61

The rats on the CVP diet retained 15 times as much sodium as did the controls, but their myocardial and serum sodium levels differed little from control values. Their myocardial calcium rose 12%, but their serum calcium remained essentially unchanged. Their myocardial magnesium and potassium levels dropped 19 and 33%, respectively; serum values of both cations dropped about 20% (Sos, 1965; Table 6-4).

6.2.1.5. *Other Cardiovasopathic Models That Might Entail Relative Magnesium Deficiency*

Arterial lesions, similar to those produced by magnesium deficiency, in combination with high calcium, vitamin D, or fat intakes or other imbalances (i.e., CVP diet) have been produced by modalities that increase serum calcium or cholesterol

TABLE 6-5. Serum and Soft Tissue Mineral Changes in Other Cardiovasopathic Models

Experimental model	Serum levels				Soft tissue levels			
	Mg	K	Na	Ca	Mg	K	Na	Ca
Excess vitamin D, or dihydrotachysterol (± sodium phosphate)	↓	↓	↑	↑	↓	↓	↑	↑
Excess mineralocorticoids (+ sodium phosphate)	↓	↓	↑	↑	↓	↓	↑	↑
Hyperparathyroidism 2° to <Mg, <Ca, or both; exogenous	↓	↓	↑	↑	↓	↓	?	↑
Hypoparathyroidism (PT_x) (+ sodium phosphate)	±	±	±	±	↓	↓	↑	↑
Excess catecholamines: stress induced; exogenous	±	±	±	±	↓	↓	↑	↑
Myocardial hypoxia								
early	↑	↑	±	±	↓	↓	↑	↑
late	↓	↓	±	±	↓	↓	↑	↑

levels, increase tissue sodium and calcium levels, and decrease magnesium and potassium, both in the serum and in the tissues. (Table 6-5). Dihydrotachysterol, particularly in combination with sodium acid phosphate (NaH_2PO_4), causes coronary and aortic calcification and periarteritis, lesions that are intensified by magnesium or potassium deficiency, partially protected against by administration of either cation and better protected against by both and by the chloride ion. (Selye, 1958a,b; Bajusz and Selye, 1959; Mishra, 1960d). Mineralocorticoids plus phosphates produce multifocal necrosis (suggestive of small coronary disease), the intensity of which is also increased by magnesium and/or potassium deficiency; again, each cation is protective (Selye, 1958a,d,e,f; Selye and Mishra, 1958; Bajusz and Selye, 1959; Mishra, 1960b; Selye and Gabbiani, 1965). Parathyroid extract, with sodium phosphate salts (Selye, 1958c; Lehr, 1963) or stimulation of parathyroid 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. Administration of mineralocorticosteroids markedly intensifies the cardiovascular lesions of these (Lehr, 1959) and of the catecholamine myocardial necrosis model (Guideri *et al.*, 1971). Paradoxically, despite the calcium-mobilizing effect of parathyroid hormone, and the vitamin-D-like arterial damage it produces in combination with a phosphate salt, Lehr (1959) has shown that phosphate-loading of parathyroidectomized rats causes even more severe cardiovascular lesions. Subsequent work from his laboratories has demonstrated that the common denominator in the experimental models—calcium- or phosphate-loading in the presence or absence of parathyroid hormone, or with mineralocorticoid, or catecholamine (exogenous or endogenous)—is depletion of myocardial magnesium and subsequently of potassium (Lehr, 1965b, 1969; Lehr *et al.*, 1966, 1969, 1970/1972, 1976/1980). The increase of cellular calcium reflects, predominantly, the calcification of injured tissues, even in the presence of hypocalcemia of the parathyroidectomized rats. Stress has also been associated with markedly increased myocardial damage when the animals are magnesium or potassium deficient, and magnesium administration has protected against stress and exogenous catecholamine-induced cardiovascular damage (Selye, 1958g; Selye and Mishra, 1958; Shimamoto *et al.*, 1959; Mishra, 1960e; Mishra and Herman, 1960; Bajusz, 1965a). Lehr (1965, 1966) has correlated the microfocal myocardial necrosis, seen in most of the drug- and stress-related experimental cardiovasopathic models (which resemble the lesions of "pure" magnesium deficiency, *supra vide*), with damage to the cardiac microcirculation, with medial degeneration and perivascular myocardial necrosis, and has stressed the depletion of intracellular magnesium as an early and consistent change. The animals that are loaded with calcium, 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 diet). That magnesium deficiency predisposes to the hypercoagulability, and that magnesium administration has been protective, may relate to the role of magnesium in platelet function (Review: Elin, 1976/1980), as well as to the effects of magnesium on coagulation factors (Szelenyi *et al.*, 1967; Szelenyi, 1971, 1973; Stevenson and Yoder, 1972; Seelig and Heggtveit, 1974).

6.3. *Catecholamine-Induced Arterial Damage; Magnesium Interrelationships*

In addition to the increased susceptibility to atherogenesis that catecholamines can cause by inducing lipolysis, Raab (1958) called attention to the evidence that prolonged administration of small doses of epinephrine produces intimal thickening of small and large vessels of rabbits and dogs, and that larger doses produce necrotizing and calcifying lesions of the media. The similarity of these arterial lesions to those of magnesium deficiency, particularly in association with high intakes of calcium or of calcemic agents (*supra vide*), brings attention to the evidence that catecholamines cause loss of cellular magnesium. Epinephrine has been shown to increase plasma magnesium levels after its injection or after drug- or stress-induced stimulation of its secretion (Rogers and Mahan, 1959a,b; Larvor, 1968; Larvor and Rayssiguier, 1971; Rayssiguier and Larvor, 1971/1973). Catecholamine injection or its stress-induced secretion has caused lowered myocardial magnesium levels. This effect might be partially reciprocal to catecholamine-induced cellular uptake of calcium, a physiologic action that contributes to its positive inotropic effect (Nayler, 1967). The arterial damage caused by catecholamines, however, must be a pathologic extension of its activity that intensifies production of a low cellular magnesium/calcium ratio.

One mechanism might be via local hypoxia mediated by proliferative constrictive endothelial proliferation, in conjunction with its increase of oxygen consumption (Raab, 1969). It should be recalled that even short-term local hypoxia, such as is produced by occluding the vessels by a blood pressure cuff can cause increased plasma magnesium, presumably as a result of egress of cellular magnesium (Whang and Wagner, 1966; S. P. Nielsen, 1969). Thus, this mechanism, too, can produce a low Mg/Ca cellular ratio.

The general increase in blood pressure that is the classic response to catecholamine release or injection must also be considered. The cardiac output increases as a result of increased strength of myocardial contraction and increased heart rate [both contributed to by the catecholamine-stimulated shift of calcium into the heart (Nayler, 1967)], and secondary to the increased venous return to the heart, as splanchnic, renal, skin, and mucosal arterioles constrict.

The protection by magnesium against intimal damage (*supra vide*) might serve to protect the arterial lining from the mechanical stresses caused by sudden changes in pressure and local oxygenation. There are experimental data suggesting that magnesium deficiency increases some of the catecholamine effects on the arteries, and that magnesium excess tends to counteract them. For example, Hanenson (1963) found that absence of magnesium from the medium in which aortic slices were suspended markedly increased the contractile response to norepinephrine; its addition decreased the contractile response. However, recent work on interrelationships of magnesium and calcium with vasoactive hormones on vascular muscle has elucidated the magnesium dependence of the reactions and explained how magnesium depletion can cause refractoriness to vasoactive hormones (pages 179–183). *In vivo* rat studies have shown that slow intravenous infusion of magnesium sulfate

decreases the hypertensive response to epinephrine or norepinephrine (Cession *et al.*, 1963). The influence of magnesium deficiency or excess on release of catecholamines is considered under our discussion of magnesium and the heart. In this regard, the demonstration that arterial tissue exhibits rapid uptake of catecholamines (particularly of epinephrine) even when injected within the range that is probably produced by catecholamine-releasing agents, such as nicotine, stress, hypoglycemia, or thyroid hormone (Raab and Gigee, 1958) is probably relevant to the clinical situation.

A high-fat diet that was thrombogenic (incorporating propylthiouracil and cottonseed oil) became cardiopathic when NaH_2PO_4 was added (Savoie, 1972a,b, 1975). Since the findings with this regimen, and with modifications of the electrolyte steroid cardiac necrosis (ESCN) syndrome developed by Selye (*supra vide*), including catecholamines and exposure to stress, point predominantly to effects of drugs and minerals (predominantly magnesium) on cardiac metabolism (Savoie, 1971a,b, 1975) *infra vide*.

6.4. *Magnesium Deficiency, Mast Cells, and Arteriosclerosis*

Still another change has been seen in the cardiovascular tissues of both atherosclerotic experimental animals and patients, and in experimental magnesium deficiency: decreased numbers of mast cells and evidence of degranulation. It has been suggested that connective tissue mast cells may play a role in the development of arteriosclerosis (Constantinides, 1953; Cairns and Constantinides, 1954; Wexler, 1964). Evidence for this theory derives from the observation that rats, a species resistant to atherosclerosis, has many mast cells in the myocardium, whereas susceptible rabbits (Constantinides, 1953) and chickens (Padawar, 1957) have few mast cells. Furthermore, young women have more mast cells than do young men and atherosclerotic patients have fewer mast cells than do normals (Hellstrom and Holmgren, 1950; Constantinides and Cairns, 1954). Wexler (1964) has reported that the number of myocardial mast cells was most severely depressed in breeder rats that developed the most severe spontaneous arteriosclerosis, and that mast cells were not found in the vicinity of the arteriosclerotic lesions. Their granules showed a marked change from metachromasia to orthochromasia, which was interpreted as indicating secretory discharge. The decrease in numbers of mast cells in arteriosclerotic arteries has been correlated with the decrease in hyaluronic acid in arteriosclerotic arteries (K. Meyer *et al.*, 1959; Kaplan and Meyer, 1960; Buddecke, 1962). Since mast cells secrete hyaluronic acid (Padawer, 1957), the decrease in number of mast cells in arteriosclerosis may explain the decline in hyaluronic acid content. Experimental magnesium deficiency has also been shown to cause decreased tissue mast cells, and to increase their degranulation (Bélanger *et al.*, 1957, Bois *et al.*, 1960; Hungerford, 1964; Hungerford and Bernick, 1976/1980). More data are required to ascertain whether the decreased numbers of mast cells in animals and patients with atherosclerosis might be contributed to by magnesium deficiency.

6.5. *Arterial Resistance, Blood Pressure, and Magnesium*

The term "hypertensive-arteriosclerotic cardiovascular disease" reflects the frequent association of what are actually two separate diseases: hypertension and arterio-, or more commonly, atherosclerosis. That hypertension can lead to arterial damage has been accepted for many years, although the mechanisms are still subject to dispute. This is not the place to consider the experimental evidence and hypotheses that suggest that hypertension can predispose to formation of atherosclerotic by damaging the endothelium and permitting diffusion of cholesterol into the intima (Haust, 1970), e.g., at sites of swirling and eddying of the blood stream (Duff, 1951), as a result of pressure-induced arterial dilatation (Schornagel, 1956; Helin *et al.*, 1971). It is, however, pertinent that each disorder has been found in magnesium-deficient models, most commonly in combination.

The mechanism of the morphological changes produced in the blood vessels by magnesium deficiency is not clear, but the changes almost certainly contribute to the increased arterial resistance. A contribution by vasoconstriction also seems likely, particularly since magnesium deficiency (experimental) is usually associated with decreased serum concentrations of magnesium, potassium, and in soft tissues, decreased content of magnesium and potassium and increased content of calcium and sodium. Depending on whether the magnesium deficiency is associated with intake of calcemic agents, the serum calcium can be either low, normal, or high. When it is high, the electrolyte imbalance is one that has been shown to increase arterial resistance *(infra vide)*. Increased plasma renin activity, blood serotonin level, and urinary aldosterone excretion have also been noted in magnesium deficiency—all factors that also increase arterial resistance.

The effect of magnesium deficiency on blood pressure involves complex interactions. Although most of the experimental models are associated with increased blood pressure, there are both clinical and experimental circumstances in which no effect, or actual lowering of blood pressure has been seen with magnesium deficiency. Insight into these paradoxical findings derives both from *in vivo* magnesium-deficiency studies and from *in vitro* investigations that have elucidated several aspects of the response of the vascular smooth muscle contractility and resistance to changes in magnesium and calcium concentrations.

6.5.1. *Increased Arterial Resistance: Low Mg + K, High Ca + Na*

Among the experimental models of cardiovascular disease are several that are characterized by decreased magnesium levels, and that are associated with increased arterial resistance. The magnesium-deficient animals that develop hypertension, as well as arterial and cardiac damage, usually also have hyperlipidemia, atheromata, and hypercalcemia. Animals with vitamin D toxicity, or those given the CVP diet *(supra vide)*, fall into this category. Only in one study, in which the relative dietary intakes of magnesium and calcium were changed, did the blood pressure of calcium-deficient, magnesium-adequate rats show a greater decline than did that of magnesium-deficient rats (Itokawa *et al.*, 1974b).

Acute studies, in which a low ratio of magnesium, potassium, or both, to calcium is produced by intra-arterial infusions, have shown that such a ratio (particularly in the presence of alkalosis) increases arterial resistance in peripheral, renal, and coronary circulation (Haddy, 1960, 1962; Haddy *et al.*, 1963, 1969; J. Scott *et al.*, 1961, 1968; Frohlich *et al.*, 1962). On the basis of the experimental findings, Haddy and Overbeck (1962) and Frohlich *et al.* (1964) suggested that such electrolyte imbalances might be a common denominator in clinical hypertension. They cited hypercorticism, hyperparathyroidism, vitamin D toxicity, and eclampsia as diseases characterized by hypertension and often by such electrolyte abnormalities. Similar acute intraarterial infusion studies with normotensive and hypertensive human subjects yielded comparable results (Overbeck *et al.*, 1969). The most recent reviews consider the physicochemical interrelationships among the cations and the arterial contractile processes (Altura and Altura, 1977a,b; Haddy and Seelig, 1976/1980). Calcium plays a central role in excitation–contraction coupling and this ion competes with magnesium for binding sites on the membrane of the vascular smooth muscle cell. When extracellular magnesium falls, more calcium is available on the membrane for entrance into the cell with each spike potential. Furthermore, the number of spike potentials may increase because lack of magnesium and potassium suppresses the sodium–potassium pump, which, because of the electrogenic nature of the pump, leads to a decrease in the resting membrane potential. Increased membrane calcium and number of spikes would elevate intracellular calcium and cause vasoconstriction.

The magnesium concentration of the medium in which arterial strips are suspended affects their contractile response to vasoactive drugs and hormones. In its absence, potent contractile responses have been produced (Altura, 1970, 1975a,b; Altura and Altura, 1971, 1974, 1976/1980, 1978; Altura *et al.*, 1976/1980), an action that might be attributable to the greater surface binding of calcium when there is no competition by magnesium for common binding sites (Altura and Altura, 1971, 1974; Turlapaty and Carrier, 1973; Jurevics and Carrier, 1973). Somlyo *et al.* (1972) have proposed that incubation of arterial strips in magnesium-free solutions reversibly blocks the hyperpolarizing effect of cyclic AMP. Altura and Altura (1977, 1978) have hypothesized that these acute effects of changes in extracellular ionic magnesium result from effects on calcium permeability, translocation, and membrane stability, as well as from competition for binding sites. In fact, as with other tissues, exposure of vascular smooth muscle to low extracellular magnesium concentrations has resulted in increased tissue calcium content (Altura and Altura, 1971; Palaty, 1971, 1974). It can be speculated that reciprocal changes in serum and tissue calcium seen in magnesium-deficient animals (Review: Seelig and Haddy, 1976/1980) might be mediated by these mechanisms. Altura and Altura (1974) have provided evidence from their *in vitro* studies that withdrawal of ionic magnesium from the suspending medium produces arterial muscle contraction that is due to the inward movement of calcium. When a chelating agent (Ca EDTA) that selectively removes magnesium is added to the medium, the arterial muscle contracts; when one that selectively chelates calcium (EGTA) is added, the arterial muscle relaxes (Altura and Altura, 1975). Carrier *et al.* (1976) have shown that magnesium has two components in its interaction with calcium: (1) competition at extracellular sites, prob-

ably at the membrane; and (2) intracellular competition at sequestration sites. They confirmed the increased tension of arteries in a potassium-free medium (Hendrick and Casteels, 1974) and showed that magnesium decreases arterial sensitivity to calcium in both high- and low-potassium solutions, but increases the maximum calcium-induced response in high-potassium solution.

Changing magnesium and calcium concentrations affects the vasocontractile responses to hormones. At such low rates of magnesium infusion in dogs as to barely affect arterial resistance, the arterial contraction produced by injected catecholamines was substantially reduced (Haddy, 1960; Frohlich *et al.*, 1962). Suspension of arterial strips in media lacking both calcium and magnesium resulted in almost no contractile response to such agents as acetyl choline, angiotensin, or epinephrine; restoring the calcium but not the magnesium markedly increased the vascoconstriction (Altura and Altura, 1978, 1976/1980) (Fig. 6-5).

The converse effect, that of the vasodilatory effect of high magnesium concentrations (Haddy, 1960; Haddy and Scott, 1965; Scott *et al.*, 1968; Overbecke *t al.*, 1969), seems to be mediated by displacement by magnesium of calcium bound to the cell surface. This has been shown to inhibit calcium influx and to uncouple excitation from contraction in myocardial cells (Langer *et al.*, 1968; Shine and Douglas, 1974), and is probably also true for vascular muscle. Possibly, in this circumstance, the excess magnesium that displaces calcium from surface binding sites allows for fewer depolarizations and less contractility. Also to be considered is the possibility that high levels of magnesium markedly decrease the hypertensive response to angiotension II, as has been shown in rats (Cession *et al.*, 1963).

6.5.2. *Magnesium Deficiency and Decreased Blood Pressure; Refractoriness to Vasoactive Hormones*

In contrast to the above observations, and in conflict with the "logical" explanation of mechanisms by which magnesium deficiency causes vasoconstriction and its excess causes vasodilation, there is both experimental and clinical evidence that magnesium deficiency has caused decreased blood pressure (Fig. 6-6). The demonstration by Cantin (1970, 1971/1973a,b) that magnesium-deficient rats develop a continuous increment of the juxtaglomerular index (JGI), and of the width of the zona glomerulosa of the adrenal cortex, explains the aldosteronism of magnesium deficiency reported by Ginn (1968) but not the lack of hypertension in Cantin's deficient rats. He commented on the similarity of the JGI changes produced by magnesium deficiency to those reported after adrenalectomy, sodium deficiency, or renal ischemia (Cantin, 1971/1973a), and considered it plausible that increase in the JGI and the widening of the adrenal cortical zona glomerulosa might reflect response to a shift of fluid from the vascular space (with decreased circulating volume), as occult edema developed (Cantin, 1970, 1971/1973b). He suggested that since the rise of the JGI and the adrenal cortical changes developed early (by the 15th day) in his magnesium-deficient rats, the shifts in sodium and potassium content of serum and urine, and the subsequent marked edema (by the 25th day) might indicate stimulation of the renin–angiotensin–aldosterone system (Cantin, 1970). It was postulated that the JGI and adrenal cortical changes were probably mediated by diminution of

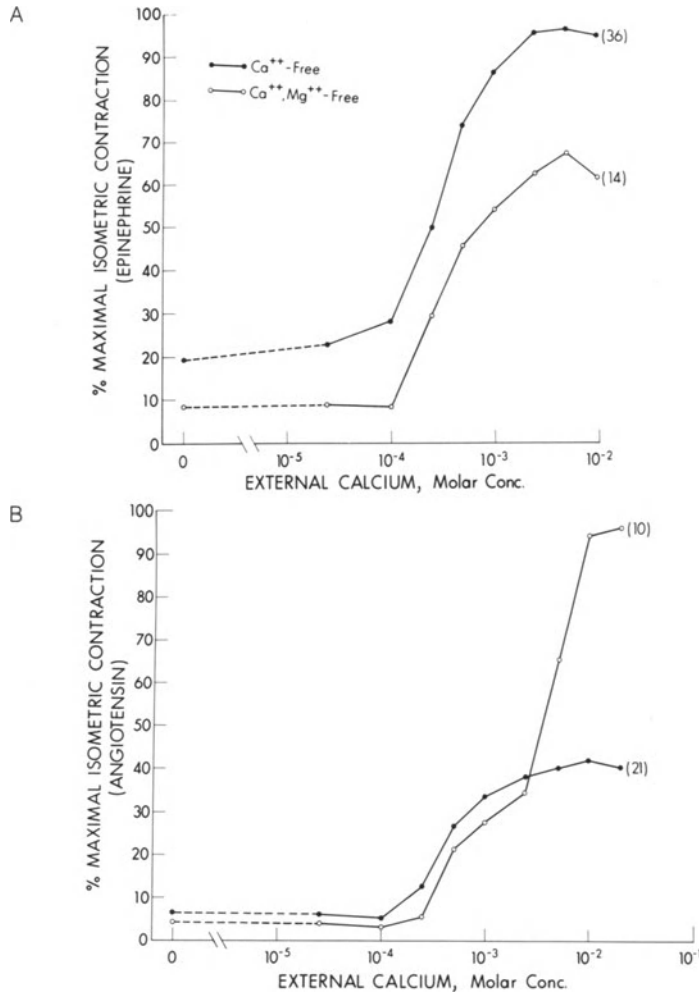

FIGURE 6-5. Calcium restoration dose–responses of rat aortic strips, with and without magnesium in medium. A: Angiotensin-induced contractions. B: Epinephrine-induced contractions. (From BM Altura and BT Altura: *Blood Vessels* 15:5–16, 1978.)

the arterial pressure of the renal afferent arterioles, which led to stimulation of the renin-secreting, granular cells of the juxta-glomerular area, with subsequent angiotensin production and stimulation of aldosterone secretion (Cantin, 1970; Cantin and Huet, 1973). In the magnesium-deficient rats of Dagirmanjian and Goldman (1970), the systemic blood pressure was unaffected. They found the blood flow to be diminished by as much as 50% in most organs in the deficient rats that survived 40 days, but that there was splanchnic (gut and liver) vasodilatation that earlier had balanced the visceral vasoconstriction (in terms of systemic blood pressure). Early blood flow changes in these rats included increased flow to the adenylhypophyseal area.

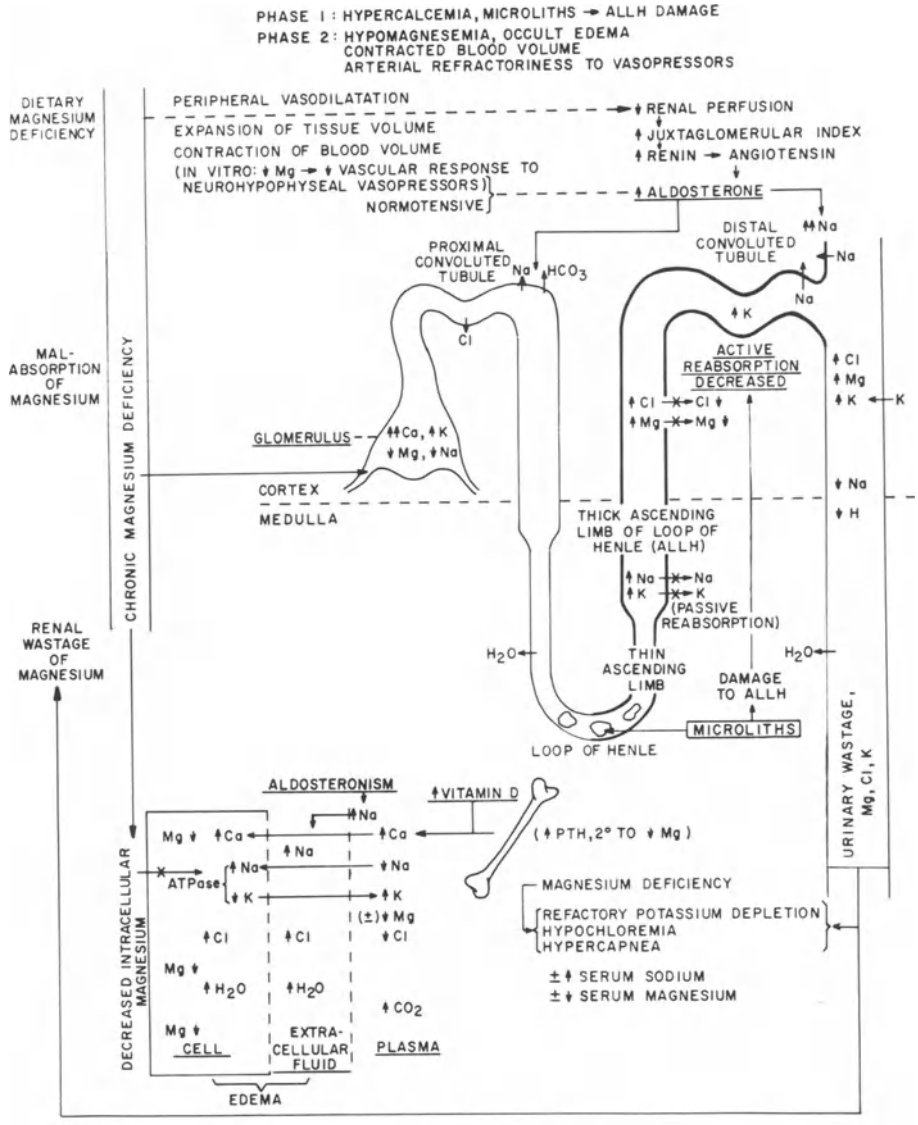

FIGURE 6-6. Magnesium deficiency with normotensive aldosteronism.

It is suggested (Haddy and Seelig, 1976/1980) that this might be a response to the decreased activity of neurohypophyseal peptides in magnesium deficiency. For example, it has been suggested that magnesium potentiates the contractile response of isolated vascular smooth muscle to vasopressin, oxytocin, and vasotocin, the action of which is magnesium dependent (Somlyo *et al.*, 1966; Somlyo and Somlyo, 1970). Altura (1975a,b; Altura and Altura, 1977) have elucidated the mechanisms by which magnesium enhances the vasoconstrictor response to the vasoactive peptides. Thus, in the absence of optimal magnesium concentrations, the arteries

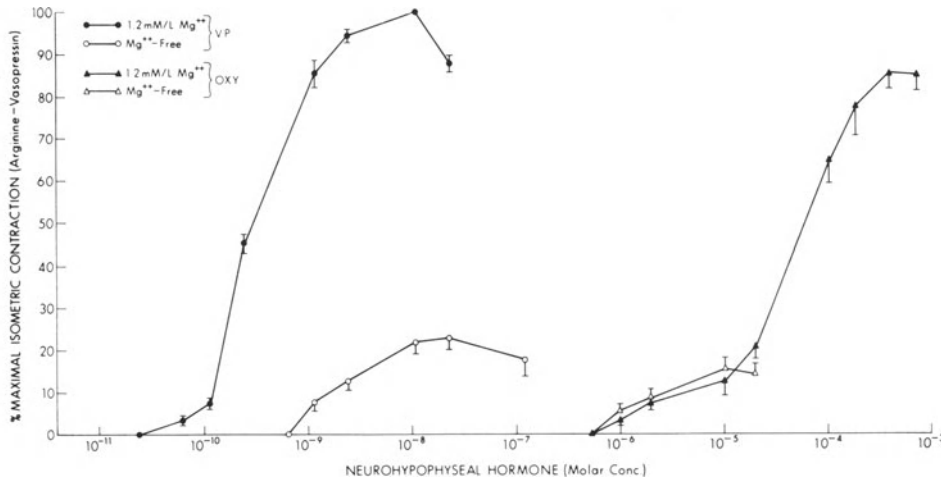

FIGURE 6-7. Dose–responses to neurohypophyseal hormones of rat aortic strips with and without magnesium. Cumulative dose–response curves of [8-arginine]vasopressin and oxytocin in Krebs–Ringer bicarbonate with and without 1.2 mM Mg^{2+}. ●——●, Vasopressin with added Mg^{2+}; ○——○, vasopression without $[Mg^{2+}]_o$; ▲——▲, oxytocin with added Mg^{2+}; Δ——Δ, oxytocin without $[Mg^{2+}]_o$. Each curve represents an average of at least 12 different rat aortic strips. (From BM Altura: *Am J Physiol* 28; 1615–1620; 1975).

exhibit refractoriness to high levels of the neurohypophyseal peptides. In fact, Altura (1975) clearly showed that the isometric contraction in response to vasopressin was markedly diminished in the absence of magnesium, as compared to its response in the presence of normal magnesium concentration (Fig. 6-7). Responsiveness to angiotensin was absent when both calcium and magnesium were missing from the medium; it was greatly increased when the calcium was restored in the absence of magnesium (Altura and Altura, 1976/1980b). This observation confirms the early *in vivo* observation that calcium but not magnesium is necessary for angiotension-II-induced hypertension (Cession *et al.*, 1963).

Still another magnesium–vasoactive hormonal interrelationship has been elucidated by Altura *et al.* (1976, 1976/1980). They have shown that without optimal magnesium in the bath fluid suspending isolated rat arterial muscle, prostaglandin cannot evoke arterial muscle relaxation.

6.5.3. Clinical Magnesium Deficiency and Blood Pressure

With so many magnesium-related factors influencing arterial contractility, it is not easy to select those that will precipitate either hypo- or hypertension, or produce symptomatic signs of magnesium deficiency without notably affecting the blood pressure. The most dramatic changes in blood pressure mediated by magnesium are (1) the rise that has occurred during iatrogenic hypomagnesemia, produced by replacement of gastrointestinal and renal losses by magnesium-free fluids, which have been lowered by magnesium repletion (Smith *et al.*, 1960; Smith, 1963; Hall and Joffe, 1973); and (2) the hypotension seen with severe hypermagnesemia (Mordes *et al.*, 1975). Less frequently noted is the hypotension of severe magne-

sium depletion as in children with the recovery syndrome of protein calorie malnutrition (Caddell, 1965, 1967).

In general, gradual or chronic changes in serum magnesium levels are not associated with marked changes in blood pressure. On the other hand, note should be taken of the hypomagnesemic form of aldosteronism (Mader and Iseri, 1955; Milne *et al.*, 1957) that is usually associated with moderately to markedly elevated blood pressure. In contrast, a woman has been reported who had marginal magnesium deficiency, occult edema, signs of latent tetany, and subnormal blood pressure, with intermittent aldosteronism and hyperreninism (Seelig *et al.*, 1975, 1976/1979), a syndrome much like that reported by Cantin in rats (Cantin, 1970, 1971/1973).

Whether magnesium deficiency contributes to the hypertension of children with the supravalvular aortic stenosis syndrome that is associated, not only with hypercalcemia, but hyperlipidemia and that has been associated with hyperreactivity to vitamin D (Reviews: Black, 1964; Beuren *et al.*, 1962, 1964, 1966; Seelig, 1969b; Seelig and Haddy, 1976/1980) remains to be ascertained. There have been a few instances of hypomagnesemia reported, but the use of milk of magnesia to control the common constipation of this syndrome makes it difficult to interpret the rare reports of magnesium levels. Hypertension and hyperlipidemia have been reported in children and adults with hypervitaminosis D (Frost *et al.*, 1947; Lang and Eiardt, 1957; DeLangen and Donath, 1956; Beuren *et al.*, 1964, 1966; and 24 cases in Appendix Table VIa; low serum magnesium levels have been reported only rarely (Frost *et al.*, 1947; Lowe *et al.*, 1954). Dalderup (1960) speculated that the damage of infantile hypercalcemia might be related to cellular magnesium deficiency. Other conditions associated with hypercalcemia and hypomagnesemia in which hypertension is not uncommon include hyperparathyroidism (Pyrah *et al.*, 1966) and hemodialysis with "softened" water (Schulten *et al.*, 1968).

The relationship of the magnesium status to adult hypertensive syndromes is difficult to ascertain. Most of the emphasis has naturally been on sodium/potassium exchanges. The potentiation of the pressor effects of catecholamines by corticosteroids, which was demonstrated by Raab, and correlated with the transmembrane Na/K gradient and blood pressure regulation (Raab, 1959), can also be referred to as regards magnesium/calcium shifts. Both hormones cause magnesium egress from the cells; catecholamines also increase calcium influx.

As has been discussed, hypomagnesemia is common in preeclampsia and eclampsia, and hypotensive as well as anticonvulsive response to magnesium therapy in pharmacologic doses is anticipated. However, still to be proved is whether these responses reflect repair of a deficit or merely vasodilation in response to a pharmacologic agent. Similarly the use of magnesium to control hypertensive crises of renal disease (during the diuretic phase) requires resolution as to mechanism. In hypercalcemic hypertension, renal damage may complicate the diagnostic problem.

As regards essential hypertension, the common use of diuretics that cause renal magnesium loss makes interpretation of serum magnesium levels difficult. Holtmeier (1969b) has surveyed cardiovascular and other complications of diuretic treatment of hypertension that might result from magnesium loss and recommends its repletion.

7
Magnesium Deficiency/Loss from Myocardium

The foregoing section has dealt predominantly with the evidence that magnesium deficiency can be contributory to arterial lesions (culminating either in sudden death or in chronic atherosclerosis) that are implicated in the cardiovascular diseases of civilization. Raab (1972), in his introduction to a symposium on myocardiology, commented that the current "official" approach to the problem of degenerative heart disease represents adherence to "traditional but outdated concepts that imply a purely, or almost purely coronary vascular origin of fatal myocardial lesions." He referred to evidence that in about half the deaths clinically attributed to "myocardial infarctions," "coronary occlusions," "coronary thrombosis," or "coronary artery disease," no thrombi or vascular occlusions were found on autopsy (Baroldi, 1969, 1970/1972; Spain and Bradess, 1960). He suggested that the term "coronary heart disease" be replaced by one referring to "cardiac hypoxic dysionism," as encompassing the ionic myocardial changes produced in association with the myocardial hypoxia resulting from a decreased oxygen supply (coronary insufficiency) in conjunction with stress-induced hormonal (catecholamine) increased oxygen demand (Raab, 1969). As depicted in Fig. 7-1 (Raab, 1972), hypoxia causes decreased myocardial concentrations of both magnesium and potassium and increased myocardial sodium. This dysionic pattern is contributed to by stress-induced corticosteroid secretion.

When myocardial levels of magnesium fall, there are many contributory factors. That nutritional imbalances leading to general magnesium deficiency, such as have been described in the introductory chapter on epidemiology, can contribute and can reduce the resistance of the myocardium to stress and to noxious agents seems likely. It might be the extra magnesium that is provided by hard water that is responsible for the much lower incidence of sudden death from ischemic heart disease (IHD) in residents of hard-water areas, as compared with the IHD sudden-death rate in soft-water areas. It is possible that water-magnesium is sufficient to correct (at least partially) the marginal magnesium deficiency that has been shown to be prevalent and increasing in the United States and in Europe. The lower

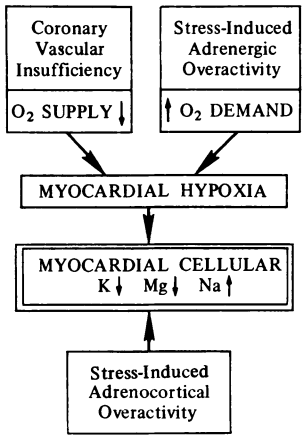

FIGURE 7-1. Central position of low K and Mg and high Na in myocardial cells in stress-induced cardiomyopathy. (From W Raab: *Recent Advances in Studies on Cardiac Structure and Metabolism: Myocardiology*. E Bajusz and G Rona (Eds), University Park Press, Baltimore, 1972, pp 707–713.)

myocardial and coronary magnesium levels found in accident victims in soft-water areas, as compared with those found in comparable subjects in hard-water areas, indicate that an insufficient magnesium intake is reflected by lower myocardial magnesium levels (T. Crawford and M. D. Crawford, 1967; T. Anderson *et al.*, 1973, 1975,1976/1980). It is important to note that despite the difference in myocardial magnesium levels, plasma magnesium levels in residents of soft- and hard-water areas are the same (T. Anderson *et al.*, 1975, 1976/1980). This is another indication of the unreliability of plasma magnesium as an indication of the total status of magnesium or of its level in vital organs.

7.1. Cardiac Magnesium Lability

Although, on the grounds of logic, one would expect the heart to retain magnesium with avidity—since substantial loss of myocardial magnesium is incompatible with life—cardiac magnesium is actually quite labile. Rogers and Mahan (1959 a,b) reported that in the exchange of plasma magnesium with tissues, there are rapidly and slowly exchangeable forms of magnesium in the tissues of rats. In the heart, liver, and kidney, the exchange was rapid, reaching equilibrium in about three hours. In cows and calves, the equilibration was slower than in rats, but liver, kidney, heart and pancreas similarly showed most rapid exchangeability of ^{28}Mg (Rogers *et al.*, 1964). Page and Polimeni (1972), also working with rat hearts, have demonstrated that about 98% of ventricular cellular magnesium is exchanged at the same but relatively slow rate [disagreeing with Rogers and Mahan (1959 a,b) that the exchangeable portion was "rapidly" exchangeable]. They found that only 2–3% is inexchangeable (Page *et al.*, 1972), in contrast to that of skeletal muscle, 75–80% of which is exchangeable (Gilbert, 1960). They found that the rate of myocardial magnesium exchange is 0.15 ± 0.02 mM Mg/minute/kg^{-1} dry ventricle or about 0.21 ± 0.02 pmol/sec/cm^{-2} of plasma membrane. The rate of exchange is independent of the rate of contraction or the external work done by the ventricle (Polimeni

and Page, 1973a,b, 1974). Measurements of the influx and efflux of magnesium and the very low passive permeability of myocardial cells to magnesium suggested that there is probably a carrier-mediated mechanism for its cardiac transport that might be capable of preventing development of unphysiologically high myocardial cellular levels of magnesium (Page and Polimeni, 1972). Most of the 98% of exchangeable myocardial magnesium is presumably present as Mg complexes of the adenine nucleotides: ATP, ADP, and AMP. Less than 15% is associated with the mitochondria or myofibrils (Polimeni and Page, 1973a). The mitochondrial mechanism of magnesium transport has been shown *in vitro* to cause accumulation of large amounts of magnesium by transporting it across the inner mitochondrial membrane into the matrix (Brierley *et al.*, 1962; Brierley, 1967; 1976). More recent studies show that there are mitochondrial ionophores that mediate magnesium (and other ions) transport (Green *et al.*, 1975) and that such ionophores have been identified in heart mitochondria (Blondin, 1974, 1975). In rat ventricles all of the mitochondrial magnesium is exchangeable with ^{28}Mg given intraperitoneally (Page and Polimeni, 1972), and so possibly this may be a means of regulating the amount of ionic magnesium in the cytoplasm. *In vivo,* myocardial cells accumulate a proportional increase in magnesium in response to stimuli that cause cellular hypertrophy (such as mechanical constriction of the ascending aorta); under such conditions there is also a disproportionate increase in sequestered myofibrillar magnesium (Page *et al.*, 1972). Polimeni and Page (1973b, 1974) comment that a constant cellular magnesium concentration is essential to the myocardial cell. They observe that since a major proportion of cellular magnesium is complexed with the adenine nucleotides, it may be the constancy of the magnesium concentration that is related to the constancy of adenine nucleotide concentrations, which is necessary for normal myocardial cellular metabolism, including ionic exchange and energy production.

The ready exchangeability of almost all myocardial magnesium, and the demonstration of Mg^{2+}–K^{+}, specific mitochondrial ionophores that mediate myocardial mitochondrial magnesium transport, probably explain its rapid uptake, which is demonstrable when it is given as ^{28}Mg. Brandt *et al.* (1958) reported that of all the soft tissues and viscera analyzed from 24 to 48 hours after ^{28}Mg administration (i.v. infusion to rats), the heart took up the greatest proportion of the isotope. [The kidneys, liver, and pancreas took up less, but much more than did the other tissues studied (Fig. 7-2)]. They suggested that finding such marked avidity for the magnesium, in tissues with high enzyme activity, was not surprising, in view of the importance of magnesium in ATP and other enzyme systems (Lehninger, 1950; Green and MacLennan, 1960). The heart's uptake of ^{28}Mg has been shown to be ten times as rapid as that of skeletal muscle (Brandt *et al.*, 1958; Aikawa *et al.*, 1959; Field, 1961; Field and Smith, 1964). In view of their demonstration of the particular avidity of dogs' hearts for ^{28}Mg in dogs, Glaser and Brandt (1959) extended the study to calves and rabbits. The findings were consistent in the three species. They found the greatest avidity for ^{28}Mg in the interventricular septum and in the left ventricle of calves. The authors postulated that the high ^{28}Mg uptake of the septum might reflect the requirement of the conduction system for impulse transmission. The greater septal and left ventricular uptake of ^{28}Mg than in the rest of the heart was reaffirmed in dogs (Glaser and Gibbs, 1962). Lazzara *et al.* (1963) confirmed the

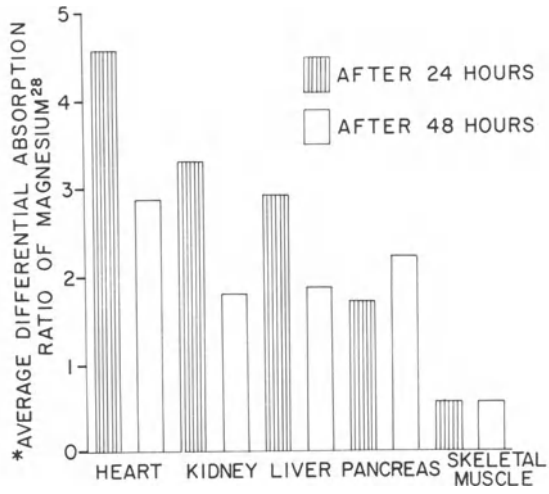

FIGURE 7-2. Soft tissue uptake of ^{28}Mg after infusion. *Calculated as the ratio of isotope concentration to the concentration obtained if the isotope were uniformly distributed in the body. (Derived from Brandt *et al.*, 1958.)

avidity of ventricles and septum for tagged magnesium at 46, 56, and 68 hours after its i.v. administration in dogs. It is of interest that in an analysis of different portions of the heart (of dogs), Burch *et al.* (1965) found the highest cardiac concentrations of magnesium in the interventricular septum, epicardial myocardium, and ventricles. Rogers *et al.* (1964) did not specify the portions of the heart scanned, but included that organ as one of those with the highest specific activity 2–6 hours after injection of ^{28}Mg into cows and calves.

In magnesium-deficient rats, the relative specific activity (the ratio of the specific activity of the tissue to that of plasma) of heart and other metabolically active organs (e.g., kidney, liver, glandular tissue) reached peak levels within 2–3 hours after injection of ^{28}Mg, and remained high through the 22 hours of the study. The values declined after an initial rise in control rats (Field and Smith, 1964). Comparison of magnesium-deficient and control rats given ^{28}Mg before sacrifice at intervals up to 48 hours, showed rapid uptake (at 2–4 hours) that was most marked in liver, heart, and kidney (Chutkow, 1965). All subcellular fractions of the myocardium, from rats kept magnesium deficient for 32 days, exhibited avidity for ^{28}Mg that had been given 12 hours before sacrifice (Ryan *et al.*, 1973). Rats that had been repleted for 18 days before the ^{28}Mg injection did not show greater than control ^{28}Mg uptake, indicating repair of the myocardial deficit within that period of time.

7.2. The Magnesium Status of the Myocardium

The amount of myocardial magnesium might be the factor that determines cardiac response to the many cardiopathic factors in our environment. Dietary imbal-

ances that increase magnesium requirements at the same time that less is ingested have been shown to lower myocardial magnesium levels. In experimental animals, such short- or long-term magnesium deficiencies have produced arrhythmias, coronary arterial lesions, and light- and electron-microscopic evidence of damage that is intensified by stress. Hormones that stress causes to be secreted (e.g., catecholamines and corticosteroids), and drugs or hormones that cause further loss of magnesium, particularly when associated with retention of calcium (e.g., diuretics, digitalis, vitamin D, dihydrotachysterol), have similar effects.

This brings us to the concept of "pluricausal cardiomyopathy," a term used by Selye (1961, 1969) and Raab (1969, 1972) as preferable to the limiting term "coronary heart disease." They used it to encompass also hormonal and dysionic responses to emotional, as well as drug-induced stresses and metabolic aberrations. Selye (1969) commented that deficiences in dietary potassium, magnesium, or chloride each predisposes to cardiac necrosis closely resembling that of his electrolyte-steroid cardiac-necrosis (ESCN) experimental model in that all produce extensive, usually multifocal myocardial necrosis. Excessive concentrations of epinephrine-like substances in the heart of a young athlete who had died suddenly (Raab, 1943a), and in hearts of patients who had died with angina pectoris and other cardiac dysfunctions (Raab, 1943b), and the similarity of the ECG changes of patients with IHD to those of animals or humans given epinephrine, led Raab to consider stress-induced hormonal (catecholamine and corticosteroid) excess as basic to the disorder he termed cardiac "dysionism" (Raab, 1972). He observed that major shifts in myocardial electrolytes can lead to disturbances in cardiac rhythm, contractility, structure, and ultimately to cell necrosis. His emphasis was on the depletion of intracellular potassium, but he observed that this was usually paralleled by loss of glycogen and magnesium and by entry of sodium into the myocardial cells.

Since experimental magnesium deficiency was first recognized as causing cardiac damage, both functional and morphological, and since development of the electron microscope has permitted demonstration of mitochondrial changes (remarkably similar to those produced by experimental ischemia) that can explain the dysionism referred to by Raab (1969, 1972), the cardiac changes caused by magnesium deficiency are presented before the discussion of the role of magnesium loss in dysrhythmias.

7.3. Myocardial Changes with Magnesium Deficiency or Loss (Animal)

7.3.1. Experimental Magnesium Deficiency

Functional and histologic abnormalities of the heart were demonstrated in magnesium-deficient rodents and ruminants over 40 years ago (Greenberg *et al.*, 1936; Moore *et al.*, 1936) and low cardiac magnesium levels in the failing human heart even earlier (Wilkins and Cullen, 1933). The nature of the damage that is caused by experimental magnesium deficiency, and the protective effects of magnesium administration, have been demonstrated in many animal models of cardiovascular

disease (Reviews: Selye, 1958g; Bajusz, 1965; Heggtveit, 1965c, Raab, 1969; Lehr, 1969; Rigo, 1971; Rotman, 1971; Szelenyi, 1971; Seelig, 1972; Seelig and Heggtveit, 1974; Seelig and Haddy, 1976/1980). As indicated, the "pure" magnesium deficient heart has histological myocardial lesions that are predominantly perivascular (around the damaged small coronary arteries) and thus probably reflect hypoxia secondary to the early arterial damage.

Light microscopic lesions (including focal myocardial necrosis, exudative inflammation, and varying degrees of calcification and collagen deposition) were seen in rats that were magnesium depleted for 14–36 days, the degree of damage being directly related to the duration of the depletion (Heggtveit *et al.*, 1964; Heggtveit, 1965b,c). A group that was also cold stressed (swimming in ice-water bath for four minutes) twice daily the last two days before sacrifice exhibited the most severe damage; they were the only rats to exhibit grossly evident cardiac damage. Many of the myocardial lesions were perivascular, surrounding small ramifications of the coronary arteries, but this was not a consistent finding. Primary arterial damage, other than edema of the endothelium, was not noted. Ultrastructural changes in the myocardium were most pronounced in and around the areas of necrosis. Like the magnesium-deficient rats reported by Nakamura *et al.* (1961) that had swollen mitochondria after 12 days of magnesium deficiency, those of Heggtveit *et al.* (1964) also showed mitochondrial or sarcosomal swelling and distortion (at 14 days). There was vacuolization of enlarged sarcosomes, clumping of cristae, and progressive deposition of electron-dense material, which eventually filled the entire saracosome or mitochondrion especially in the magnesium-deficient stressed rats (Fig. 7-3). Rats given the same diet, but with magnesium supplements, developed no cardiac lesions, whether or not they were cold stressed.

Fragmentation and loss of myofilaments (which make up the myofibrils) both accompany and follow the sarcosomal changes. Thus, there is disruption of "Z" bands and "M" lines, with spaces within the myofibers. Aggregating within these spaces (corresponding to vacuoles seen by light microscopy) are dilated components of the sarcoplasmic reticulum, damaged sarcosomes and ground substance, lipid droplets and glycogen particles. Finally, the sarcolemmal membrane ruptures or disappears, and the altered sarcoplasmic constituents spill into the interstitial space, where they are ingested by macrophages aligned alongside necrotic muscle cells (Heggtveit, 1965c).

Mishra (1960b), who had found that the mitochondrial fraction of hearts from magnesium-deficient rats was diminished, reasoned that such a loss, which is linked to oxidative phosphorylation, might be responsible for defective ability of magnesium-deficient mitochondria to maintain ionic gradients and for metabolic and respiratory cell injury leading to myocardial necrosis. DiGiorgio *et al.* (1962) proposed that since the amount of magnesium in the distorted cardiac sarcosomes was the same (or even more) in the magnesium-deficient than in the control rats, possibly it was in a form unsuitable for coupling of oxidation to phosphorylation.

Ultramicroscopy has shown that magnesium deficiency for as little as 12–14 days has caused cardiac mitochondria to swell (Nakamura *et al.*, 1961; Heggtveit *et al.*, 1964; Heggtveit, 1965b,c); that such swelling is not physiologic, such as occurs during ionic flux (Fig. 7-4A), but is pathologic (Fig. 7-4B). It is associated

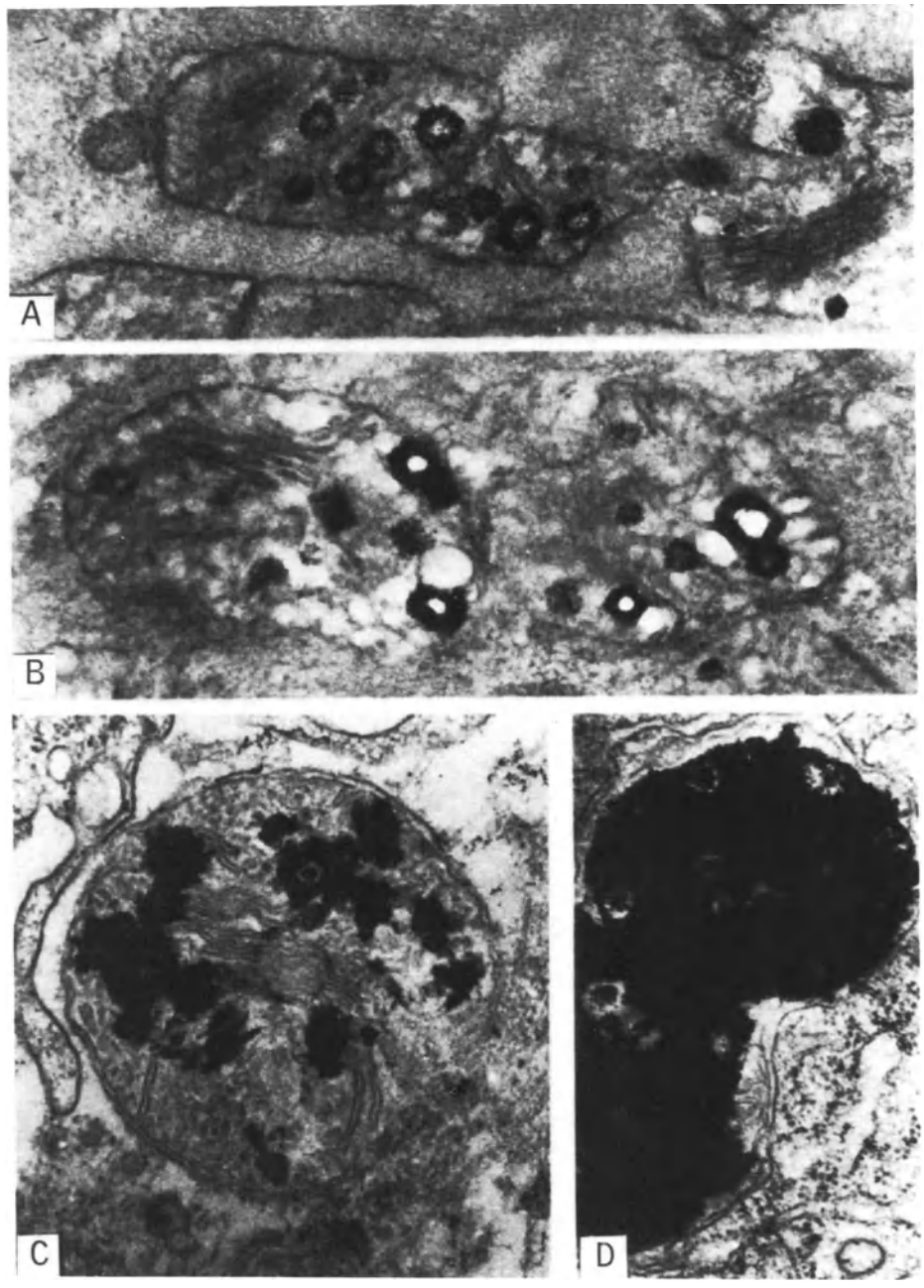

FIGURE 7-3. Mitochondrial granules in magnesium-deficient stressed rats and progressive filling of mitochondria with electron-dense granules, presumably calcium. × 32,000 (reduced 6 % for reproduction). (A) Day 23: The dense granules are, at first, arranged as spheres with clear centers. (B) Day 23: The spheres become thicker and more dense. (C) Day 29: Electron-dense granules increase in number and appear as solid dense particles. (D) Day 29: Eventually the entire sarcosome is filled with tightly packed particles. (From HA Heggtveit *et al.: Am. J Path* 45:757–782, 1964.)

with mitochondrial disruption and disorganization. The electron dense particles probably consist of calcium (e.g., as phosphate crystals). Possibly some of the mitochondrial magnesium is similarly made unavailable (Jennings, 1969; Seelig, 1972). Such redistribution of the calcium and magnesium ions, taking them and the inorganic phosphate out of the pool available for oxidative phosphorylation, might be contributory to irreversible mitochondrial damage. It must be noted that the mitochondria from a magnesium-deficient rat that had marked mitochondrial and sarcosomal calcium granular deposition (Heggtveit *et al..*, 1964; Heggtveit, 1965b,c) were from a rat that was cold stressed.

Heggtveit (1965c) has reviewed the data correlating the close interdependence between mitochondrial structure and function and has observed that early sarcosomal alterations are fundamental to the evolution of the cardiac necrosis of magnesium deficiency (Heggtveit *et al.*, 1964). He noted that the calcium accumulation occurring in magnesium deficiency begins before the cell dies. A recent *in vitro*

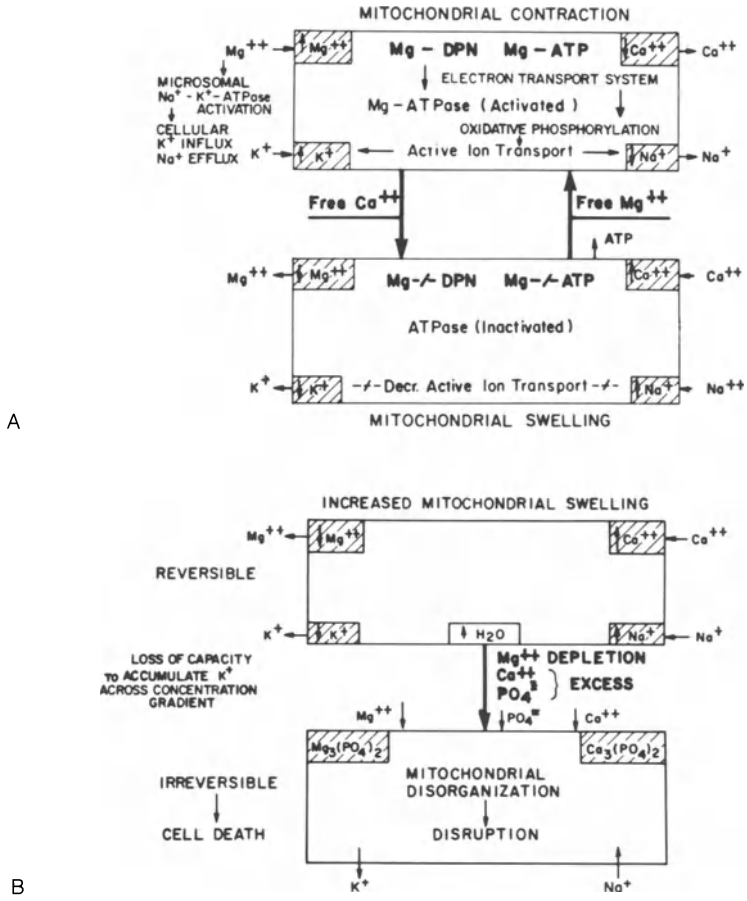

FIGURE 7-4. Mitochondrial electrolyte shifts. A: Physiologic mitochondrial processes. B: Mitochondrial changes with magnesium deficiency. (From MS Seelig: *Recent Advances on Cardiac Structure and Metabolism: Myocardiology*. E. Bajusz and G Rona (Eds), University Park Press, 1972, pp 707–713.

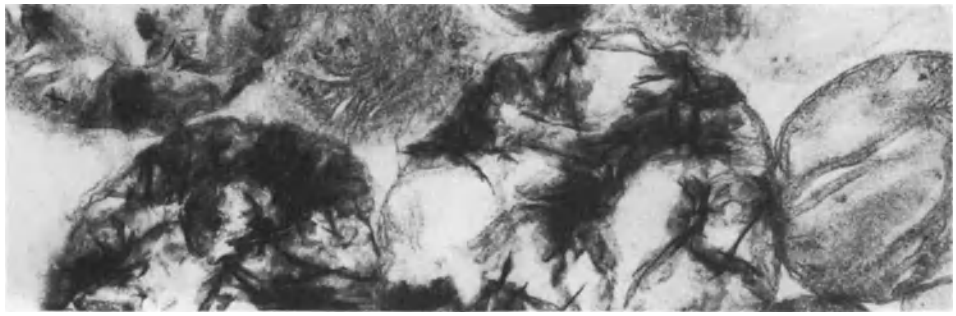

FIGURE 7-5. Mitochondrial needle-like crystals in magnesium deficiency after 1 min of calcium uptake. × 40,000 (reduced 23% for reproduction). (Courtesy of BB Silver and LA Sordahl, 1976/1980.)

study provides evidence that magnesium modulates calcium uptake in cardiac mitochondria (Silver and Sordahl, 1976/1980). Respiration-supported calcium uptake by rabbit-heart mitochondria in magnesium-free medium was almost double that in the presence of magnesium. Furthermore, in the absence of magnesium, the calcium crystals in the mitochondrial matrix were needlelike. On addition of magnesium to previously magnesium-free suspensions, they underwent transformation into an apparently destructive granular type with dendritic crystals that obliterated the internal mitochondrial structure (Fig. 7-5). In the presence of magnesium, spheroidal-amorphous calcium crystals form in the mitochondria. Silver and Sordahl (1976/1980) suggest that the magnesium modulation of the calcium uptake, and its influence on the shape of the crystals, is consistent with the protection afforded by

TABLE 7-1. Loss of Myocardial Magnesium in Cardiac Hypoxia (Laboratory Models)

Investigators	Time sample taken	Myocardial magenesium in:	
Coronary ligation (dogs)	After ligation		
Cummings and Clark (1957)	8–11 hr	Infarcted tissue	30% ↓ (vs.noninfarcted)
Cummings (1960)	8–11 hr	Infarcted ventricle	49% ↓ (vs. sham-operated heart)
		Noninfarcted ventricle	7% ↓ (vs. sham-operated heart)
Rigo *et al.* (1966)	6 days	Necrotic area	21% ↓ (vs. intact area)
		Perinecrotic area	9% ↓ (vs. intact area)
Jennings (1969); Jennings and Shen (1972)	40 min, then reflow		29% ↓ (vs. control heart)
	60 min		1% ↓ (vs. control heart)
Asphyxia (guinea pigs)	Duration, min		
Hochrein *et al.* (1967)	0.5		15% ↓ vs. control
	1.0–1.5		31% ↓ vs. control
	2.0		33% ↓ vs. control
	2.5–4.0		34% ↓ vs. control
	8.0		30% ↓ vs. control
	10.0		25% ↓ vs. control
	10.5		7% ↓ vs. control
Hemorrhagic hypotension (dogs)	After bleeding	Right ventricle	Left ventricle
Canepa *et al.* (1965)	135 min	8% ↓ vs. control	14% ↓ vs. control
	180 min	21% ↓ vs. control	29% ↓ vs. control

TABLE 7-2. Loss of Myocardial Magnesium (Percentage Decrease) in Cardiac Ischemia (Human)[a]

Myocardial infarcts		
Iseri *et al.* (1952)	Infarcted segment	42%
	Noninfarcted segment	33%
Meister and Schumann (1962)	Infarcted heart	19%
Raab and Kimura (Cited by Raab, 1969)	Noninfarcted segment	32%
Heggtveit *et al.* (1969)	Infarcted segment	42%
	Noninfarcted segment	19%
Carbon monoxide poisoning		
Laurendeau and DuRuisseau (1963)		23%
DuRuisseau (1971–1973)		
Induced cardiac arrest		
in surgery		
Cardiac surgery		
Singh *et al.* (1972)	Myocardial biopsy	2–19%

[a] From control, noninfarcted hearts (autopsy).

magnesium against the necrotizing effects of calcium on myocardial cells when magnesium levels are low (Janke *et al.*, 1975; Lehr *et al.*, 1975).

7.3.2. *Magnesium Loss from the Hypoxic Heart*

There is loss of myocardial magnesium from hearts of experimental animals with coronary ligations after asphyxia (Table 7-1) and from infarcted areas of human hearts (Table 7-2). Why the drop in myocardial magnesium was greater after transient ischemia (following reestablishment of circulation) than it was in dog hearts with permanent ischemia (Jennings and Shen, 1970/1972) was not explained, but it is in accord with the short-term (up to 10 minutes) findings of Hochrein *et al.* (1967) with asphyxiated guinea pigs and with the long-term study of electrolyte changes in infarcted versus noninfarcted areas of the heart from 5 hours at intervals to 30 days (Table 7-3, Matyushin and Samartseva, 1972). It is conceivable that the short-term fall in magnesium, reaching almost normal levels 2½ minutes after cardiac arrest, might reflect formation of unavailable (possibly phosphate precipitate) magnesium within the mitochondria (Seelig, 1972).

Jennings *et al.* (1965,1969) have shown that myocardial cells show some mitochondrial damage (some loss of cristae and matrices), some loss of glycogen and some margination of chromatin material within 15 minutes after coronary occlusion. Restoration of blood flow by no more than 18 minutes allowed for resumption of normal structure and function (back to aerobic from anaerobic metabolism). Longer periods of ischemia resulted in irreversible mitochondrial damage, with loss of cristae, disruption of limiting membranes, and intramitochondrial granules (after 40 minutes of ischemia). The dead or dying cells exhibit loss of magnesium, potassium, and acid-soluble phosphate, and gain of sodium, chloride, and water, an electrolyte distribution similar to that of extracellular fluid (Jennings *et al.*, 1969, 1970). Later, the calcium and phosphorus levels rise (Jennings and Shen, 1970/1972; Shen

and Jennings, 1972), probably as calcium phosphate granules form. Jennings (1969) has suggested that crystallization or binding of essential co-factors such as phosphate, calcium, and possibly magnesium in the granules might contribute to irreversible mitochondrial failure. A. Schwartz (1971/1972) commented that mitochondria have the ability to sequester large amounts of calcium, and that if enough calcium interacts with the mitochondrial membranes, there is significant uncoupling of oxidative phosphorylation. Shen and Jennings (1972) demonstrated that ischemic injury causes abnormal calcium uptake as dense intramitochondrial granules, which are an important feature of irreversible cellular injury.

The later, lesser rises in myocardial magnesium that occur in hypoxic hearts probably must be otherwise explained than by accumulation of magnesium phosphate crystals or granules in the mitochondria. Page *et al.* (1972) have shown that myofibrillar magnesium and mass increases, and the ratio of mitochondrial volume to cell volume decreases in rabbit hearts with mechanical interference with left ventricular outflow. If such myofibrillar sequestration of magnesium occurs in the surviving cells in the area in which ischemia has been induced, perhaps this explains at least partially the later rise in myocardial magnesium levels.

Heggtveit (1965c, 1969) and Heggtveit and Nadkarni (1971), in their reviews of electron microscopic findings of myocardial ischemia, considered the similarities in mitochondrial changes to those of magnesium depletion and catecholamine cardiopathy, which Lehr and his associates had correlated with early loss of myocardial magnesium and accumulation of calcium (Lehr *et al.*, 1966; Lehr, 1969). Heggtveit (1969) pointed out, however, that early nuclear changes are characteristic of ischemic injury, whereas nuclear chromatin clumping occurs only late, after severe sarcoplasmic damage of magnesium deficiency. He commented that correlation of ultrastructural data with biochemical findings confirms the importance of catecholamine release and ionic shifts (early loss of magnesium, potassium, and phosphate with influx of calcium, sodium, and water) in the early evolution of ischemic myocardial damage. Poche (1969) reported that capillary endothelial swelling, with reduction in luminal caliber of the microcirculation, is significant in the pathogenesis

TABLE 7-3. Loss of Myocardial Magnesium and Changes in Myocardial Phosphorus and Calcium[a]

Time after ligation	Mg[b]	Ca[b]	P[b]
5 hr	12 <	16 <	177 >
1 day	24 <	422 >	171 >
3 days	22 <	464 >	246 >
7 days	20 <	156 >	38 <
12 days	34 <	140 >	11 <
20 days	23 <	136 >	37 <
30 days	8 <	123 >	31 <

[a] From Matyushin and Samartseva (1972).
[b] Percent less than (<) or greater than (>) noninfarcted area.

of multifocal hypoxic myocardial necrosis. Such endothelial swelling has been reported in magnesium deficiency (Heggtveit 1965c; Hungerford and Bernick, 1976/1980), as have endothelial and medial proliferation. These arterial changes of "pure" magnesium deficiency, thus, might contribute to the hypoxia-like myocardial lesions seen in magnesium deficiency, and might contribute to the decreased resistance of the myocardium to stress factors, such as Heggtveit (1969) suggested might "condition" a chronically ischemic heart to severe response to subsequent acute episodes.

7.3.3. Magnesium Loss from the Stressed Heart or in Association with Catecholamine Administration

Raab (1943b, 1966, 1969) was the first to point out that catecholamines increase cardiac work and oxygen consumption to the extent that relative hypoxia is produced, particularly in the presence of coronary disease that prevents adequate oxygenation. Relative cardiac hypoxia is also produced with cardiac overload (Hochrein and Lossnitzer, 1969) with similar consequences: stress-induced dysionic status in the myocardium, which leads to functional and finally structural abnormalities in the heart that can result in sudden death from arrhythmias, cardiomyopathies that can lead to chronic heart disease, or the more widely recognized "coronary heart disease." Although he placed major emphasis on the loss of potassium from myocardial cells, he observed that rats stressed by isolation also had low myocardial magnesium levels (Raab *et al.*, 1968), and that patients who had died with ischemic heart disease also had low myocardial magnesium levels (Raab, 1969). He considered the catecholamine release a major mediating cardiopathic response to stress, but called attention to evidence that catecholamine mobilization of free fatty acids from adipose tissues is dependent on the presence of glucocorticoids (Maickel *et al.*, 1966). Thus, he considered the stress release of catecholamines and corticosteroids additive in cardiopathic potential.

It is thus particularly unfortunate that acute coronary occlusion is a very stressful event that stimulates secretion of both of the major groups of adrenal hormones, those of the cortex and the medulla. As regards the catecholamines, such secretion takes place, not only from the adrenal medulla, but also within the heart itself, which synthesizes, stores, and releases norepinephrine (Raab and Gigee, 1955; Braunwald *et al.*, 1964).

Much work has been done on the nature of the gross, histological, and electron-microscopic myocardial necrosis produced by high doses of the potent β-adrenergic amine, isoproterenol, since the work of Rona *et al.* (1959), which was shown the same year to be intensified by mineralocorticoids (Chappel *et al.*, 1959). Ferrans *et al.* (1964, 1969), using the high dose (85 mg/kg) that consistently produces large infarction-type lesions, found that mitochondrial swelling, vesiculation, and crystolysis developed early, and myofibrillar degeneration later. Zbinden and Bagdon (1963) found that even with relatively low doses, the myocardial lesions occurred regularly and were located predominantly at the interventricular septum, the apex, and the wall of the left ventricle. The location of the lesions at the sites that had been shown to have the greatest affinity for ^{28}Mg (Glaser and Brandt, 1959; Glaser and Gibbs, 1962) and to have the highest magnesium concentration (Lazzara *et al.*,

TABLE 7-4. Myocardial Electrolytes in Rats: Isoproterenol in Dose Causing Microfocal Necrosis[a]

	Cardiac levels (mEq/kg wet wt)			
	Normal controls	After isoproterenol injection		
		3 hr	7 hr	24 hr
Magnesium	19.2 ± 0.3	17.0 ± 0.08	16.3 ± 0.3	15.6 ± 0.3
Potassium	83.6 ± 0.8	83.0 ± 1.5	83.0 ± 1.5	81.3 ± 1.0
Sodium	44.1 ± 0.6	42.4 ± 0.9	47.1 ± 1.7	53.0 ± 1.3
Calcium	2.8 ± 0.2	3.8 ± 0.1	4.8 ± 0.1	4.3 ± 0.3
Phosphorus	57.6 ± 0.1	53.9 ± 0.6	53.6 ± 1.9	48.1 ± 1.5
	Incidence of cardiac necrosis			
Mild		25%	90% (+)	0
Severe	0	0	0	100% (3+ to 4+)

[a] From Lehr *et al.* (1966).
[b] $p \leq 0.01$.

1963; Burch *et al.*, 1965), and the similarity of the ultramicroscopic lesions to those produced by magnesium depletion are inferential evidence that the catecholamine-induced myocardial might be mediated by loss of myocardial magnesium. Lehr *et al.* (1966), using small enough doses of isoproterenol (5.25 mg/kg) to produce disseminated myocardial necrosis, rather than grossly evident necrosis, proved the first myocardial changes to be loss of magnesium and phosphorus increased calcium; sodium and potassium changes occurred later (Table 7-4). The decrease in magnesium in the myocardium was demonstrable as early as one hour after isoproterenol injection, even preceding the mitochondrial changes that were evident at two hours. In view of the importance of magnesium in oxidative phosphorylation, it is not surprising that similarly small doses of the catecholamines caused its depression in cardiac mitochondria (B. Sobel *et al.*, 1966).

There is another magnesium/catecholamine interrelationship that should be considered. Magnesium and calcium have reciprocal effects on storage or release of catecholamines from adrenergic granules in the adrenal medulla. Mg-ATP stimulates amine incorporation in adrenal medullary granules (Carlsson *et al.*, 1963). Calcium stimulates and magnesium inhibits release of catecholamines from the granules. (W. Douglas and Rubin, 1964; J. Burn and Gibbons, 1964). Since catecholamine granules, epinephrine, or related substances have been demonstrated in the myocardium (Raab, 1943a,b; Potter and Axelrod, 1963b), particularly in hearts from patients with angina pectoris (Raab, 1943b), the observation that *in vitro* addition of magnesium stabilizes the catecholamines in the heart, preventing releasing of norepinephrine, (Potter and Axelrod, 1963a) might be significant in the clinical situation.

In his thesis on the effects of magnesium deficiency in the rat, C. Johnson (1965) showed that the adrenal medullary levels of epinephrine fell: 23% decrease after 8 days of deficiency and 46% decrease after 12 days of deficiency. Possibly this reflects increased release of epinephrine from the adrenal medullary granules in magnesium deficiency. The same rats also exhibited a slight increase in myocardial

catecholamine levels that was associated with low cardiac magnesium and ATP levels.

7.3.4. Corticosteroid + Phosphate-Induced Myocardial Necrosis

In addition to the increased output of catecholamines in response to stress, the secretion of corticosteroid hormones is also increased. Selye approached the problem of cardiovascular disease associated with stress from the standpoint that mineralcorticoid secretion was predominantly to blame, particularly in subjects with dietary excesses of sodium, phosphate, and sulfate (Review: Selye, 1958f). In the historical introduction to his 1958 monograph, Selye referred to the early work on the importance of ionic interactions for the function of cardiac muscle *in vitro,* which led to the recognition of the advantages of physiologically balanced perfusion electrolyte solutions over saline. He reviewed the discovery that had been made at the turn of the century of "acute interstitial myocarditis" for which no cause was identifiable, and commented on the similarity of those lesions to those discovered about the same time (1904) to be produced by experimental overdosage with cardiac glycosides. When irradiated ergosterol preparations became available in 1929, he found that intoxication with sterols of the vitamin D group also produces generalized arterial calcification and focal myocardial necrosis and calcification (Selye, 1929). He noted that all of these myocardial disorders, including that caused by potassium deficiency (Schrader *et al.,* 1937) were characterized by focal necrosis and by inflammatory infiltration (similar to that reported by others using magnesium-deficient diets, *supra vide*). Then he found that multiple doses of the mineralocorticoid desoxycorticosterone (DOC) caused minute myocardial necrosis in rats, an effect attributed to loss of potassium (Darrow and Miller, 1942). Chicks, fed a ration that was rich in sodium chloride, were more susceptible to DOC-cardiotoxicity (and nephrotoxicity) (Selye and Stone, 1943), and sodium chloride aggravated myocardial necrosis caused by potassium deficiency (Cannon *et al.,* 1953). Selye (1958f) noted that in the "control" potassium-deficient rats in the latter studies, the chloride salt of magnesium had been used as a "filler," in place of the sodium salt, magnesium's protective role not then being generally known. Development of the electrolyte (sodium phosphate)-steroid (mineralocorticoid)-cardiac necrosis (ESCN) model permitted demonstration of some of the factors that intensified or mimicked the myocardial, noninfarctoid lesions. It also permitted investigation of factors with cardioprotective properties (Selye, 1958f). Sodium salts of phosphate and sulfate intensified the lesions; magnesium and potassium chlorides were protective (Selye, 1958 a,d,g, 1961, 1969, 1970b; Selye and Mishra, 1958; Selye and Gabbiani, 1965). Because the ESCN-like lesions could be produced by unrelated agents—cardiac glycosides, vitamin D derivatives, epinephrine, stress—as well as by deficiencies of magnesium or potassium or both, Selye postulated that there must be a common pathway. Also noted was the efficacy of chloride salts of magnesium and potassium against many cardionecrotizing agents (Bajusz and Selye, 1960a). In his surveys of the evolution of the concept that stress contributes to cardiovascular diseases, Selye (1961, 1970a,b) described experiments that, depending on conditioning factors, including stress and the "stress hormones" (ACTH,

corticosteroids, and the catecholamines), can produce or prevent cardiovascular lesions. He investigated the importance of mineralocorticoids in the pathogenesis of hypertension, edema, and myocardial lesions (in animals and in human disease) and showed that glucocorticoids that lack a significant mineralocorticoid component do not intensify the ESCN. It is noteworthy that chronic hypercorticism that is associated with sodium and water retention is associated with renal loss of both potassium and magnesium (Review: Massry and Coburn, 1973), and thus functions to increase levels of the "conditioning" cation, sodium, while causing loss of the "protective" cations, potassium and magnesium.

That such a combination of responses can have serious consequences is indicated by the extraordinary potentiation of acute isoproterenol-cardiotoxicity by pretreatment with DOCA and saline (Guideri *et al.*, 1971,1974,1978). Such conditioning of the rats resulted in death from fibrillation within 15 to 30 minutes after 150 μg/kg to 0.1 mg/kg of isoproterenol subcutaneously, an amount far below the minimally toxic dose (5 mg/kg) used to produce microfocal necrosis in earlier studies of isoproterenol alone (Lehr *et al.*, 1966; Lehr, 1969) or in combination with mineralocorticoids (Chappel *et al.*, 1959). The myocardial electrolyte pattern showed significant accumulation of sodium and loss of potassium, magnesium, and phosphate. As for the glucocorticoids, the secretion of which is also increased in stress, they further contribute to the metabolic abnormalities by the dependence of catecholamine metabolization of free fatty acids on their presence (Maickel *et al.*, 1966).

Catecholamine levels were not measured in the magnesium-deficient rats (dietary magnesium: 12 mg/g diet for seven weeks) that had much greater degrees of cardiac necrosis when cold stressed than did control cold-stressed rats fed a standard magnesium-supplemented deficient diet (Mishra, 1960e; Heroux *et al.*, 1971/1973). In the latter series (Heroux *et al.*), four of the eight stressed rats also had 1+ to 2+ cardiac damage (compared to 1+ to 3+ cardiac lesions in all seven of the magnesium-deficient rats). The investigators considered the possibility that the control diet might have been suboptimal in magnesium, and that the control rats might resemble humans on suboptimal magnesium intakes in their susceptibility to myocardial damage of stress.

7.3.5. Hereditary Cardiomyopathy of Hamsters

An interesting model of genetic cardiomyopathy, developed in dystrophic hamsters, might help in elucidating some of the myocardial interrelationships with magnesium and catecholamines. These hamsters, that consistently develop focal myocardial degeneration and myolysis between the 30th and 40th days of life, exhibit decreased magnesium and increased calcium in their myocardium even before the lesions develop (Bajusz and Lossnitzer, 1968), and increased levels of cardiac norepinephrine not long thereafter (Angelakos, 1968; Table 7-5). The low magnesium levels did not persist, but the calcium levels rose markedly in the 56- to 71-day-old cardiomyopathic hamsters, at a time when the norepinephrine levels had risen further (Angelakos, 1968; Angelakos *et al.*, 1970–1972). By the time heart failure had ensued (120 days), the norepinephrine levels had dropped to half the

TABLE 7-5. Myocardial Magnesium, Calcium, and Norepinephrine in Cardiomyopathic Hamsters

Myocardial (mEq/kg wet wt)	23–33 days[a]		56–71 days[a]	
	Control	Cardiomyopathic	Control	Cardiomyopathic
Mg	115 ± 2.33	73 ± 0.80	109 ± 0.98	109 ± 1.25
Ca	12.1 ± 0.51	17 ± 0.46	14.6 ± 0.44	215 ± 33.90
K	16.3 ± 0.49	15.4 ± 0.65	13.8 ± 0.22	13.9 ± 0.34
Na	309 ± 4.8	303 ± 2.2	316 ± 4.5	307 ± 6.3
	35 days[b]		55 days[b]	
Heart norepinephrine (μg/g heart)	0.99	1.18[c]	1.03	1.28 ($p < 0.05$)

[a] Derived from Bajusz and Lossnitzer (1968).
[b] Derived from Angelakos (1968).
[c] $P<0.05$; no significance in later studies (Angelakos *et al.*, 1972).

control (young animal) levels, but to a quarter that of the same-age controls (Angelakos, 1968). Cardiac catecholamine stores also decrease once heart failure develops in other experimental models and in human heart disease (Angelakos *et al.*, 1969).

7.3.6. Stress and Free Fatty Acids/Myocardial Necrosis and Magnesium

That catecholamines exert a lipolytic effect and increase circulating free fatty acids has been considered earlier. The significance of this on the response of the heart can be considerable. Balazs *et al.* (1962) and Balazs (1972) have shown that injected catecholamines or stress-induced catecholamines secretion is much more likely to cause serious myocardial damage in obese than in normal rats. This supports the contention that catecholamine-induced lipolysis can be a significant risk factor, especially in overweight patients.

Although free fatty acids can be utilized by the myocardium as an oxidative substrate, there is growing evidence that high levels of free fatty acids (e.g., mobilized by catecholamines) are cardiotoxic (Rosenblum *et al.* 1965; Opie, 1969; Hoak *et al.*, 1970–1972) and can interfere with myocardial function, especially in association with hypoxia (A. Henderson and Sonnenblick, 1970, 1970/1972; Shug and Shrago, 1973). Opie (1969) has evaluated the relative importance of glycolytic and fatty acid metabolism of the heart, and points out that with excesses of fatty acids and triglycerides, there is substantially increased cardiac oxygen consumption. This can intensify the relative myocardial hypoxia caused by stress, especially in the presence of coronary insufficiency.

The possibility that high levels of free fatty acids in the blood might contribute to symptoms of alcoholics by binding magnesium has been mentioned earlier, as has the favorable response to magnesium of hyperlipemic patients with occlusive arterial disease (Seelig and Heggtveit, 1974). It is possible that postinfarction

arrhythmia might be related either to excessive catecholamine release in response to the stress of the cardiac injury, or to catecholamine-induced increase in circulating fatty acids. The catecholamines are apt to lower the cardiac magnesium levels; the free fatty acids might bind magnesium in the blood. Perhaps increased myocardial lipids, such as have been attributed to catecholamine-lipid mobilization in rats injected with sympathomimetic agent (Ferrans *et al.*, 1964; 1969) and in the ESCN model, (Prioreschi, 1966), might be the result of inactivation by the intramyocardial fats of cellular magnesium. Direct evidence that a variety of dietary fats (corn oil, peanut oil, olive oil, pork fat, butter, and chicken fats, as well as saturated and unsaturated fatty acids) greatly increase the sensitivity of the rats to ESCN has been provided (Selye, 1961; Selye *et al.*, 1969).

The cardiovasopathic diet developed by Sos and his co-workers that produces spontaneous myocardial infarctions includes saturated fats and hyperlipemic and hypercalcemic nutrients. Although the diet produces only minor serum electrolyte changes it substantially lowers myocardial magnesium levels. A similar diet, which was described as thrombogenic and which resembles the diet developed by Vitale and his co-workers to produce atherogenesis, incorporates propylthiouracil and cottonseed oil; when Na_2HPO_4 is added it causes nonocclusive infarctoid myocardial lesions (Savoie, 1972a,b, 1975). Anticholesterolemic agents lower the blood lipids, but are ineffective in protecting against the myocardial necrosis (Savoie, 1972b). The potassium-sparing agents (triamterine and spironolactone), and, to a lesser degree, potassium chloride, are partially protective against the cardiac lesions but not against the hyperlipidemia; only magnesium chloride prevented the cardiac necrosis (Savoie, 1972b). Similarly, amiloride, another potassium-sparing agent, inhibits the development of cardiac lesions produced when corn oil is added to the diets of rats on the ESCN regimen, although the protection is not complete (Kovacs *et al.*, 1969; Solymoss *et al.*, 1969). Ultramicroscopy showed that there was still evidence of myofibrillar damage and mitochondrial lipid droplets, although marked focal lipid accumulations were prevented (Kovacs *et al.*, 1969). Also, the blood lipids were not normalized (Solymoss *et al.*, 1969). Savoie (1971b) demonstrated protection against myocardial necrosis in a comparable model also for triamterene and spironolactone, the agent that blocks aldosterone under conditions of chronic hypersecretion (Massry and Coburn, 1973), such as is seen in heart disease (H. Wolff *et al.*, 1957) and in primary aldosteronism in which it has been associated with magnesium loss (Mader and Iseri, 1955; Milne *et al.*, 1957). All of these potassium-sparing agents also protect against the hyperlipidemic cardiac necrosis that is intensified by stress, epinephrine, or digitalis (Savoie, 1971a,b). Although amiloride did not prevent the lowering of myocardial magnesium in the ESCN+ corn-oil model that causes severe damage in a few days, and in fact actually lowered it somewhat (Solymoss *et al.*, 1970) the potassium-sparers (amiloride and triamterene) also exert some magnesium-sparing activity (Hänze and Seybirth, 1967; Heidland *et al.*, 1970, 1973; Walker *et al.*, 1972). Whether this effect contributed to their partial efficacy in the hyperlipidemic $+Na_2HPO_4$ model, in which they were more effective than potassium chloride, but less effective than magnesium chloride (Savoie 1972b) should be further studied. It is of interest that in this less acute model, which possibly is more similar to the situation produced by human dietary indiscretions, the addition of sodium phosphate to the hyperlipidemic diet caused

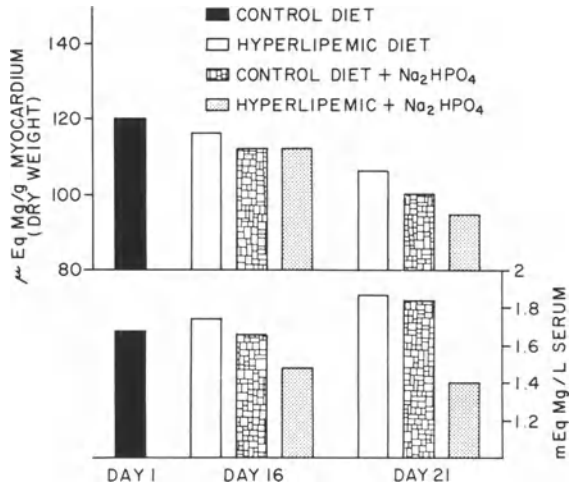

FIGURE 7-6. Myocardial and serum magnesium in rats on a hyperlipemic, thrombogenic diet, a diet loaded with Na_2HPO_4, or a diet of both. (Derived from Savoie, 1975.)

substantial lowering of both myocardial and serum magnesium levels by day 21 (Fig. 7-6, Savoie, 1975). (Note should be taken that in the hyperlipidemic and in the high phosphate-fed rats, the serum magnesium level did not reflect the drop in the myocardial levels.) Savoie (1975) considers the critical factor in the Na_2HPO_4 and hyperlipidemic rats to be their susceptibility to mitochondrial dysfunction caused by the low myocardial magnesium levels. Since the Na_2HPO_4 and the hyperlipidemia alone also lowered the myocardial magnesium levels markedly, it seems plausible that each imbalance could increase the susceptibility of the heart to stresses or other agents that further lower myocardial magnesium levels, with resultant arrhythmias or necrosis. This investigator has recently correlated the protective effect of magnesium in this model with its lowering of free cholesterol levels in the heart (Savoie and DeLorme, 1975/1980).

7.3.7. Myocardial Loss of Magnesium after Parathyroidectomy and Sodium Phosphate Load

Severe multifocal myocardial and renal necrosis, produced in parathyroidectomized rats given NaH_2PO_4, is preceded by markedly lowered myocardial (and renal) magnesium levels (Lehr *et al.*, 1966; Lehr, 1969). In addition, the microcirculation of the heart is damaged; many arterioles and precapillaries show loss of the normal architecture, with the presence of arterial and periarterial PAS-positive material. After a single NaH_2PO_4 load, there is clumping of myocardial sarcosomes, edema, and disturbances in the normal myofibrillar pattern. After two sodium phosphate loads (at 24 hours), the mitochondria are swollen and exhibit disappearance of cristae and formation of granular debris; there is also margination of nuclear chromatin. Lehr (1969) commented that the consistent, significant early shifts in

tissue cations (decreased magnesium and phosphorus, and increased sodium and calcium) in this experimental model, as well as in other very different models (e.g., catecholamines, ESCN, and cardiac overload) and the fact that the ionic shifts precede morphological damage, suggest that they are the cause, not the consequence of the myocardial damage.

7.4. *Cardiac Magnesium Loss: Central to Cardiac Dysionism, Disease, and Dysfunction (Fig. 7-7)*

As indicated in the sections on the effects of magnesium deficiency on the arteries, early damage to the small coronaries with narrowing of their lumina is characteristic of magnesium deficiency. Such myocardial arterial disease is not what is referred to by "coronary disease," but it certainly contributes to microfocal areas of hypoxia, which can give rise to the microfocal necroses, infiltration, and fibrosis that have been described in magnesium-deficient animals (Review: Seelig and Haddy, 1976/1980). It is provocative that Lehr (1965b, 1969, 1972) and his coworkers (Lehr *et al.*, 1966, 1970/1972, 1976/1980), who proposed that the loss of myocardial magnesium might contribute to the disseminated myocardial necrosis caused by dissimilar agents (including catecholamines and sodium phosphate loading of corticosteroid-treated or parathyroidectomized rats), had also implicated damage to the microcirculation (Lehr, 1965a, 1966, 1969). If magnesium nutritional deficiency or drug-induced myocardial loss is a basic contributory factor [and it has been shown to predispose also to the dysionism (decreased potassium and increased sodium), as well as to increased accretions of mitochondrial calcium (Lehr, 1969, 1972; Review: Seelig, 1972)], then Lehr was correct in both postulates.

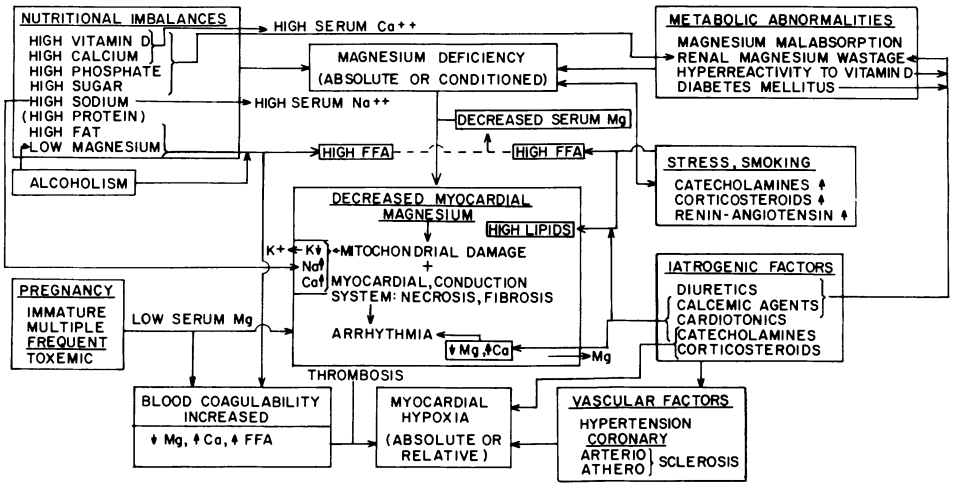

FIGURE 7-7. Central position of magnesium deficiency (dysionic "pluricausal" cardiomyopathy).

TABLE 7-6. Myocardial Magnesium in Asphyxia (Guinea Pigs)[a]

Duration of asphyxia (min)	mEq/liter	Clinical and ECG changes
0	16.6	Control
0.5	14.1	Tachycardia
1.0	11.4	Onset: hypoxic dilatation
1.5	11.4	Complete: hypoxic dilatation
2.0	11.1	AV—block I
2.5	10.9	AV—block II
4.0	10.9	AV—dissociation
8.0	11.7	Cardiac arrest (2 min)
10.0	12.5	Cardiac arrest (4 min)
10.5	15.5	Cardiac Arrest (4.5 min)

[a] Translated from H Hochrein *et al.*: *Klin Wschr* 45:1093–1096, 1967.

The loss of magnesium from the myocardium occurs so soon after hormonal or other challenge as to be suggested as a chemical means of detecting one of the earliest characteristics of myocardial damage (Lehr *et al.*, 1976/1980). Its early loss after experimentally induced hypoxia (Table 7-6, from Hochrein *et al.*, 1967) and from the heart after ischemia from coronary ligation suggests that the loss of magnesium from the fine structures of the myocardium are probably basic to the myocardial damage. Nutritional magnesium deficiency can result in early mitochondrial loss and damage directly or secondarily, as a result of focal ischemia from the narrowing of the intramyocardial vessels. Whether the hypoxia is relative or absolute, there are both increased net loss (efflux) of magnesium from myocardial cells and decreased magnesium influx during hypoxia (Polimeni and Page, 1974).

Evidence is presented that common to a wide variety of experimental models of experimental cardiomyopathy is early loss of myocardial magnesium. In his discussion of the lesions produced not only by isoproterenol, but by low doses of other catecholamines, and in other cardiopathic models [i.e., parathyroidectomy and phosphate loads, mineralocorticoid and phosphate loads (ESCN model of Selye), and hypoxic heart failure (Hochrein and Lossnitzer, 1969)], Lehr (1969) proposed that the common denominator was magnesium loss from the myocardium. He proposed that the magnesium loss is primary, and deserves closer scrutiny in view of its importance in the vital energy processes of the cell. He further proposed that its depletion might contribute to the initiation of cellular injury.

It is the premise of this section that the underlying factor—that which determines whether the individual will withstand stress or other potentially cardiopathic factors—is the adequacy of magnesium in his heart. Some might develop dysrhythmias (possibly suddenly fatal) as a result of inadequacy of the damaged magnesium-dependent mitochondrial enzyme system to maintain normal ionic equilibrium, or as the conduction system is affected or myocardial cell excitability is increased by a low magnesium/calcium ratio *(infra vide)*. Others might develop coronary arterial disease, including hypertension, and microscopic or gross myocardial lesions that lead to chronic heart disease. The foregoing section on the lability of cardiac

magnesium shows that magnesium can be readily lost from the heart, but that it can also be quickly repleted. Barnes (1962) showed that puppies kept on magnesium-deficient diets for two months lost proportionally as much magnesium from the heart as they did from bone, the major magnesium store of the body. The lower myocardial magnesium levels in residents of soft-water areas than in dwellers in hard-water areas (see Chapter 1) supports the contention that long-term suboptimal magnesium intakes are associated with loss of magnesium from the heart, and with a high incidence of sudden death from IHD.

8
Clinical Cardiac Abnormalities and Magnesium

There are several clinical conditions associated with cardiac abnormalities that resemble those produced by experimental magnesium deficiency or that cause loss of myocardial magnesium. Bajusz (1965b) refers to experimental necrotizing cardiomyopathies to describe a variety of degenerative processes that are more or less confined to the myocardium. He commented that the disease is characterized by subendocardial necrotizing foci, usually without significant disease of the coronary vessels, although comparable disorders can be produced by thrombogenic diets. He observed that "coronary heart diseases" should be classified as primary or secondary cardiomyopathies that result from vascular factors (e.g., coronary artery spasms, local microcirculatory changes), factors that directly affect myocardial metabolism and the susceptibility or resistance of the myocardium at the time of potentially cardiotoxic episodes. He pointed out that, in addition to stress situations, hormones, and age, cardiomyopathy-conditioning factors include sodium excess and deficiencies of chloride, and especially of potassium and magnesium. Bajusz (1969) has stated that the loss of these two cations from the myocardial cells (that are associated with early ultrastructural changes such as enlargement and vacuolization of the sarcoplasmic reticulum and mitochondrial degeneration) seem to be important components of many, if not all types of disturbances in cardiac metabolism, resulting in myocardial degeneration, heart failure, or fatal conduction defects.

Cardiomyopathies (and dysrhythmias not caused by diagnosed ischemic heart disease) are generally classified by clinical manifestations or by pathologic characteristics. In a criticism of any classification of primary (or secondary) cardiomyopathies that is dependent on postmortem diagnosis, Mattingly (1970) suggested that what is needed is greater effort directed toward recognition of early clinical features, search for etiologic factors, study of biochemical as well as hemodynamic alterations, and search for iatrogenic factors in the pathogenesis of and for control of this disease. Because magnesium deficiency or loss can be correlated with many

of the cardiomyopathies for which a cause has been established, perhaps it participates in those considered primary or idiopathic.

8.1. *Cardiomyopathies Not Secondary to Disease of the Major Coronary Arteries or to Infection*

The term "cardiomyopathy" was introduced by Brigden (1957) to indicate isolated noncoronary myocardial disease, present without significant disease of other systems of the body. He included instances of familial disease, amyloidosis, alcoholism, a few postpartum, and several that seemed to be due to infection. Restriction of the term to isolated myocardial disease might be unwise, since it excludes very similar cardiomyopathies associated with diseases that might provide clues to a common pathogenic factor. In subsequent surveys, the term has been used as synonymous with "myocardial disease," to indicate dysfunction of the muscular pump that is not the result of structural deformity of the heart, hypertension, or coronary atherosclerosis (Editorial, *Brit Med J,* 1969). Goodwin (1970) classifies them as congestive and hypertrophic. Hudson (1970) suggests four features that characterize cardiomyopathies: cardiomegaly, endocardial thickening, mural endocardial thrombus, and myocardial scars. He considers the fibrotic cardiomyopathies (sometimes accompanied by foci of myocardial calcification) to be likely to be related to hyperreactivity to vitamin D in infancy. He cites myocardial fibrosis in adults as the commonest form of idiopathic cardiomyopathy; it can be familial or occur as isolated cases. Hypertrophic obstructive cardiomyopathy is also familial in some instances, and Hudson (1970) considers it congenital. It is associated with narrowed outflow from either or both ventricles. Among the list of conditions that Hudson (1970) considers possibly contributory to cardiomyopathy are several in which magnesium deficiency or loss have been described: the peripartal state, infantile fibrotic cardiomyopathy, or adult endocardial fibrosis, myofibrosis (or a combination of both), alcoholism, calcium oxalosis, calcific degenerative processes, hyperparathyroidism with myocardial calcification, protein calorie malnutrition, beriberi (Oriental, or the similar, but vitamin-B_1-resistant forms seen in alcoholism and in the peripartal period), anemia, severe diarrhea, toxicity from catecholamine or cardiac glycosides, and severe trauma.

Cardiomyopathies occur throughout the world (Shaper, 1968; Editorial, *Brit Med J,* 1969). In the symposium on "Experimental 'Metabolic' Cardiopathies and Their Relationship to Human Heart Disease" (*Ann NY Acad Sci* 156, 1969), J. N. Davies (1969) discussed the African cardiomyopathies with and without endocardial lesions, and commented that none of them are confined to the African continent, as is suggested by the name. He suggested that, because coronary arteriosclerosis is so common in the United States, it is possible that many cases of cardiomyopathy are missed. This recalls Caddell's (1965, 1969b) comment that the endomyocardial fibrotic disease in Africa is prevalent in areas where protein calorie malnutrition (associated with magnesium deficiency in the recovery syndrome) is found, and her suggestion that prolonged electrolyte imbalance might be contributory.

T. James (1967) proposed that disease of the small coronary arteries might be an important contributory factor in cardiomyopathies of obscure origin, a position taken also by Varnauskas (1967). James (1967) points out that the clinical manifestations of cardiomyopathy (progressive cardiac enlargement and failure without clear cause, an inordinately high incidence of arrhythmias and conduction disturbances, syncope, sudden unexpected death, and atypical chest pain) can all be due to abnormalities of the small coronary arteries. Considering a basic abnormality to be disease of the cardiac microcirculation permits inclusion of diabetic cardiomyopathy and the cardiomyopathy of progressive muscular dystrophy (James, 1962) in the same category. Neonatal coronary arteriosclerosis-cardiomyopathy complex (Seelig and Haddy, 1976/1980) can be similarly categorized. It further substantiates the premise that loss of myocardial magnesium (and potassium) is likely to be common, not only to experimental but to clinical cardiodegenerative processes (Bajusz, 1965a; Lehr *et al.*, 1966; Lehr, 1969; Lehr *et al.*, 1976/1980), abnormalities of the myocardial microcirculation having been implicated in several of the experimental models that cause both microfocal myocardial necrosis and magnesium loss (Lehr, 1964, 1965, 1966, 1969).

There is no direct evidence that isolated or familial "idiopathic" cardiomyopathy is caused by magnesium loss or deficiency. Ultramicroscopic examination has shown some similarities to those seen in experimental magnesium deficiency and to some of the diseases in which magnesium loss has been described. For example, Hudson (1970) has examined myocardium from hypertrophic cardiomyopathy and shown sarcomeres with widely separated Z bands. Bulloch *et al.* (1972) found that myocardial biopsy specimens from 12 patients with idiopathic cardiomyopathy were similar to that associated with alcoholism.

8.1.1. Peripartum Cardiomyopathy

The etiology of peripartum heart failure is still a mystery (Editorial, *Brit Med J*, 1976a), even though it has long been recognized. It was reported in an 1848 textbook by Meigs, and myocardial degeneration was described in women who died in the peurperium by Virchow in 1870. It was reported sporadically in the first third of this century as an important factor in producing heart failure in the peripartal period (Review: Gouley *et al.*, 1937), and is now accepted as definite entity of unknown etiology that is listed as a cause of "primary" cardiomyopathy (Brigden, 1957; Hudson, 1970). The hemodynamic load of pregnancy has been implicated, but in editorial evaluations of this problem, nutritional inadequacy to meet the demands of pregnancy and lactation were considered more likely (Editorials, *Brit Med J*, 1968, 1976a).

Although magnesium deficiency has not been considered a possible nutritional factor in peripartum cardiomyopathy, there is considerable circumstantial evidence that points to magnesium depletion. Among the conditions associated with peripartal cardiac failure are those that predispose to preeclampsia and eclampsia, with which it is often associated—maternal immaturity, multiple births, and high parity—especially when rapidly successive (Hull and Hafkesbring, 1937; Hull and Hidden, 1938; Teel *et.al.*, 1937, Melvin, 1947; Szekely and Snaith, 1947; Walsh *et al.*,

1965; Govan, 1966; Stuart, 1968; J. B. Johnson *et al.*, 1966). These are all conditions that predispose to maternal magnesium depletion. Furthermore the cardiac lesions of peripartum cardiomyopathy (*supra vide*) strikingly resemble those of experimental "pure" magnesium deficiency.

Melvin (1947) and earlier Gouley *et al.* (1937) and Hull and his colleagues (1937, 1938) commented on the similarity of postpartum heart disease to cardiac beriberi, and implicated probable nutritional inadequacy. However, despite the similarity of manifestations of the disease to Oriental beriberi cardiomyopathy, it is refractory to thiamine therapy (Melvin, 1947; Stuart, 1968). This recalls the refractoriness of alcoholic "beriberi" cardiomyopathy to thiamine and to the dependence of vitamin B_1 on magnesium (p. 215). The relatively high frequency of puerperal and "idiopathic" cardiomyopathy in Jamaica, usually in patients with histories of poor nutrition (Walsh *et al.*, 1965; Stuart, 1968), recalls the early demonstration of bovine cardiovascular lesions in Jamaica that were deemed likely to be caused by a "conditioned" magnesium deficiency (Arnold and Fincham, 1950).

Review of the literature shows that the clinical picture is usually one of heart failure, presenting with shortness of breath, palpitations, edema (rarely with acute pulmonary edema), precordial pain, and embolism (Gouley *et al.*, 1937; Teel *et al.*, 1937; Hull *et al.*, 1937; 1938; Szekely and Snaith, 1947; Brigden, 1957; Meadows, 1957; S. Rosen, 1959; Benchimol *et al.*, 1959; Seftel and Susser, 1961; Gilchrist 1963; Walsh *et al.*, 1965; J. B. Johnson *et al.*, 1966; Stuart, 1968; Demakis and Rahimtoola, 1971). Diastolic, and less frequently systolic, hypertension are often found, as is cardiomegaly and abnormal ECGs. Stuart (1968) has commented that close cardiac surveillance may disclose symptomless cardiomegaly or abnormal ECG in an apparently well woman. Toxemia is commonly, but not invariably, part of the history of women who develop peripartal heart failure; Govan (1968) found that cardiorespiratory failure was the cause of fatal eclampsia in his series of 110 cases.

Hypertrophic obstructive cardiomyopathy has been reported by G. Turner *et al.* (1968) as an increasingly recognized and often familial form of cardiomyopathy of pregnancy. The Editorial (*Brit Med J*, 1968) that called attention to this now more common form of cardiac disease of pregnancy suggested that some of the young pregnant women with angina and tachycardia, with ECG abnormalities that persisted after pregnancy (Gilchrist, 1963), might have had this abnormality. This possibility calls to mind the epidemic of supravalvular aortic stenosis syndrome, and other outflow obstructive lesions, that were associated with hyperreactivity to vitamin D at the time of excessive fortification of milk with vitamin D or its use in massive parenteral dosage (Review: Seelig, 1969b) especially in the late 1940s through the 1950s. Is it possible that some of the infants so treated might have been insufficiently hyperreactive to vitamin D to develop the full-blown syndrome, but might have developed silent outflow-obstructive lesions that became overt during the peripartum period? Possibly the presumptively vitamin-D-hyperreactive women might also have had myocardial lesions as a result of the vitamin-D-induced loss of magnesium during infancy and might have been unduly susceptible to both vitamin D and magnesium deficiency during pregnancy.

There are several additional fragments of circumstantial evidence suggestive of magnesium deficiency.

1. Patients with this disease have been found to be unusually susceptible to digitalis toxicity, developing multiple premature ventricular contractions that sometimes persist (Walsh *et al.*, 1965; Demakis and Rahimtoola, 1971). (The susceptibility of magnesium-deficient dogs and monkeys to digitalis toxicity should be recalled here.) J. B. Johnson *et al.* (1966) reported an ultimately fatal case of a 14-year-old mother of twins who, because of her age and the twin pregnancy, had almost certainly been deficient in magnesium. She was unduly sensitive to digitalis.

2. In toxemia, there is commonly aldosteronism and sodium retention (A. Barnes and Quilligan, 1956), and increased catecholamine secretion (Zuspan, 1972), hormones that are secreted in excess in magnesium deficiency and that cause magnesium loss. In addition, women with preeclamptic or eclamptic pregnancies have an exaggerated response to catecholamine infusions (Raab *et al.*, 1956; Zuspan *et al.*, 1964), which have been used as a prognostic test in preeclampsia (Raab, 1957) and to differentiate between essential hypertension and toxemia of pregnancy (Zuspan *et al.*, 1964). The combination of excessive "stress" hormones with probable magnesium deficiency puts cardiomyopathy of pregnancy squarely into the category of "pluricausal" dysionic cardiomyopathy.

3. The susceptibility to peripartal intravascular coagulation, with the risks of damage to the placenta (Bonnar *et al.*, 1971) and of maternal death from embolic phenomena (Arthure, 1968) or that have been difficult to control even with anticoagulants (S. Rosen, 1959), might also be related to magnesium deficiency.

4. Among all of the cases reviewed, there was mention of use of magnesium in only two instances: one to measure circulation time, and the other in the management of eclampsia. Decherd and Herrmann (1944) commented briefly that severe tachycardia (of a woman who had had toxemia of pregnancy and developed postpartum heart failure) disappeared after diagnostic intravenous injection of magnesium sulfate. The arrhythmia later recurred and was treated traditionally. In the other instance, magnesium therapy (presumably high dosage) was given to a woman who developed eclampsia and cardiac decompensation during her fourth pregnancy (Teel *et al.*, 1937). The authors noted her "rapid recovery" and lack of recurrence of cardiac manifestations even when she returned, again pregnant, several years later. This was in contrast to five other patients with peripartal cardiomyopathy in this series: Two died and the others required digitalization, two for a short period, one of whom had persistent ankle edema and one of whom had a protracted and incomplete recovery. Whether the magnesium therapy played any role in the complete, rapid recovery of the patient remains speculative. A 38-year-old patient in this series, who died suddenly after she developed cardiac asthma and anasarca during the seventh month of her eighth pregnancy, had myocardial edema, but not necrosis, and slight subendocardial necrosis. She apparently died early in the course of the disease (possibly of arrhythmia), and thus the changes of the small myocardial arteries (intimal hyperplasia and elastica thickening) are of particular interest, since they resemble the changes of experimental magnesium deficiency.

Necropsy examination of patients who died of peripartum cardiomyopathy

generally discloses cardiomegaly and dilatation, with focal or diffuse myocardial necrosis and (in later instances) fibrosis, endocardial edema, necrosis and fibrosis and mural thrombi (Gouley *et al.*, 1937; Meadows, 1957; Walsh *et al.*, 1965; J. Johnson *et al.*, 1966; Ledingham *et al.*, 1968; Hudson, 1970; Sakakibara *et al.*, 1970). Several pathologists have reported thickened myocardial arterioles, sometimes with intimal edema or hyperplasia (Gouley *et al.*, 1937; Teel *et al.*, 1937) and perivascular infiltration around the small coronaries (Meadows, 1957).

Biopsy specimens were examined ultramicroscopically in two reported instances. Perinuclear hydropic vacuolization of myocardial fibers and sarcoplasmic fragmentation was seen 2 months before death from progressive heart failure [7 months after a twin delivery by a 14-year-old girl (J. B. Johnson *et al.*, 1966)]. A 30-year-old woman, who survived the cardiomyopathy that became manifest a week after delivery of her second baby, had widened sarcoplasmic spaces containing irregularly shaped electron-dense deposits, as well as vacuolization (Sakakibara *et al.*, 1970).

8.1.2. Infantile Cardiomyopathy

Coronary and generalized arteriosclerosis of infancy has received more attention in the literature than has infantile cardiac disease (if one excludes the valvular abnormalities and the great vessel and peripheral pulmonary atresias). However, many reporting infantile cardiovascular lesions also mention myocardial and endocardial lesions. Among the lesions tabulated (see Appendix Tables A-5A, B and A-6A, B) alone or in combination, are multifocal myocardial necrosis (such as is seen with the small coronary artery damage of magnesium deficiency, subendocardial and papillary muscle necrosis and fibrosis, and endocardial fibroelastosis, as well as massive myocardial infarctions. Among the 157 individual case reports of infants who were stillborn or who died in the first month of life, 37 had myocardial necrosis or cellular infiltration, 23 had myocardial calcinosis, and 38 had myocardial fibrosis. Among the individually cited 253 infants between 1 month and 2½ years of age, 72 had necrotic myocardial lesions, 19 had calcific lesions, and 42 had myocardial fibrosis. Endocardial fibroelastosis was reported in 83 of the infants under 1 month of age and in one-third of those of 1 month to 2½ years. Over half of the younger group of infants with EFE had outflow obstruction; only about a quarter of those between 1 month and 2½ years of age, tabulated individually, had outflow obstruction. This is in contrast to the surveys of patients selected for EFE, among whom outflow obstruction was found to be very common (Moller *et. al.*, 1964; J. Edwards *et al.*, 1965; Oppenheimer and Esterly, 1966). Perhaps a reason for the contrasting fndings is the age limitation in cases tabulated and reviewed. Congenital outflow abnormalities—whether the supravalvular aortic stenosis syndrome (SASS), aortic or pulmonic atresia or peripheral pulmonary artery stenoses (alone or in combination)—are also commonly associated with coronary, endocardial, or myocardial diseases and with hyperreactivity to vitamin D (Beuren *et al.*, 1964, 1966; Peterson *et al.*, 1965; Taussig, 1966). Subvalvular aortic stenosis has also recently been suggested as a possible result of hypervitaminosis D (McFarland *et al.*, 1978). There is a relatively small representation of children with outflow abnormalities and cardio-

facial peculiarities (which have received much recent attention as familial and isolated cases) in the Appendix tables limited to infants up to 2½ years of age. When the endocardial thickening or the arterial disease involves the septum and conducting tissue, arrhythmias and cardiac arrest might result in chronic cardiac disease or in early death. The conditions seen in those surviving beyond infancy include arrhythmias and syncopes. The implication of hypervitaminosis D in such conditions, and the description of calcification of the labyrinth in infants with outflow obstruction, with and without endocardial fibroelastosis and cardiofacies (see cited publications by Beuren *et al.*, 1962, 1964, 1966, in Appendix Table A-6B) raises the question as to whether the syndrome of deaf-mutism, prolongation of the Q-T interval, syncope, and sudden death in children and young adults (Jervell and Lange-Nielsen, 1957) (see cases 187-189, 193, 194, 203, 204, 233: Appendix Table A-6A) might be disorders in which susceptibility to vitamin D toxicity or magnesium loss or malabsorption might play an etiologic role.

In the young infants, prodromal symptoms preceded death by only a few hours to a few days. The symptoms presented are not unlike those reported for infants who died of SIDS. Some of the babies with cardiovascular abnormalities, proved at autopsy, had had signs of illness from the time of birth. ECG tracings typical of ischemic heart disease, were sometimes obtained. Those who had a subacute or chronic course generally were flaccid and quiet, behavior similar to that described by Naeye (1976a) in the SIDS. Those who did not die suddenly or after a short illness of sudden onset generally had had a fairly steady downhill course, with sustained anorexia, vomiting, weight loss, and debility. Several developed hypertension. Coronary arteriosclerosis and focal myocardial necrosis and fibrosis have been found in infants who died suddenly and in others who had been ill with clinically manifest heart disease, many of whose first cardiac manifestations developed at about two to four months of age, the age of peak incidence of SIDS. An international study of 254 cases of sudden unexpected death from cardiovascular disease (in which infants under a year of age were excluded to eliminate the SIDS) found that those who died from 1 to 5 years of age had a disproportionate representation of EFE, pulmonary stenosis, and A-V block (Lambert *et al.*, 1974). Almost a tenth of the total cases were familial. The sudden deaths of the entire series of deaths from 1 to 21 years were associated with myocardial hypoxia in half; about a third had arrhythmias.

Similar total cardiomyopathies, developing postpartum in a mother and in her 7-year-old daughter (Hudson, 1970), raises the possibility that this may have been an instance in which gestational malnutrition (magnesium?) deficiency might have caused maternal and fetal cardiac damage.

The neonatal hypoparathyroidism and hypomagnesemia of infants fed cows' milk might be the human counterpart of the model of cardiorenal necrosis, produced by sodium phosphate loading of parathyroidectomized rats (Lehr *et al.*, 1966; Lehr, 1969. Such infants have a high phosphate/magnesium ratio. Since excesses of both calcium and phosphate (relative to magnesium) are cardiopathic, the prevalence of dietary customs that lead to such imbalances perinatally and in early infancy might be contributory to cardiomyopathy of infants and young children. Persistence of such nutritional imbalances, which might become worse as the intake of high phos-

phate sodas increases, and as alcohol ingestion begins, can intensify cardiomyopathic lesions that, like the arterial lesions that receive more attention, might have their roots in infancy and possibly even before birth. Since magnesium deficiency causes damage to the intramural small coronary arteries, the perivascular damage to the myocardium that has been reported is not surprising. As in the experimental model, infants who died of cardiovascular disease typically have microfocal myocardial necrosis, infiltration, and fibrosis.

Myocardial mitochondrial and cytoplasmic changes have also been reported. Mitochondria obtained by needle biopsy of a 6-month-old boy with respiratory distress and congestive heart failure had closely stacked, parallel, concentrically arranged cristae, with some cristae filled with electron-dense granular material (Hug and Schubert, 1970). These characteristics are similar to those reported in magnesium-deficient rats (Heggtveit *et al.*, 1964; Heggtveit, 1965b,c). They were not found in the myocardium (at autopsy) of a 6-year-old girl with idiopathic cardiomyopathy, in which there was dissolution of the myofibrillar structures (Hug and Schubert, 1970). Lin (1972) described extensive mitochondrial calcification in the myocardium of a 10-week-old baby boy, who had postductal coarctation, and had had several episodes of cardiac arrest lasting 10 to 50 minutes. The intramitochondrial deposits were needle-shaped dense crystals that resemble those described by Silver and Sordahl (1976/1980) in their *in vitro* studies of cardiac mitochondria in magnesium-free medium. Lin (1972) noted that ischemia produces intramitochondrial dense bodies that probably represent calcium accumulation, and that the magnesium and potassium contents of ischemia-damaged mitochondria were reduced (Jennings, 1969). An autopsy was obtained 5 hours after the death of a 16-month-old girl who had been in good health until sudden onset of pallor and rapid pulse, with supraventricular tachycardia (320/minute), 18 days antemortem (Haese *et al.*, 1972). The heart showed numerous swollen rounded myocardial cells with partial or complete loss of contractile elements and granular or vacuolated sarcoplasm. Occasional necrotic myocardial cells had adjacent inflammatory cells. The altered cells had many lipid droplets. The mitochondria were distorted. Similar myocardial lesions had been reported in four other female infants (Ross and Belton, 1968; J. Reid *et al.*, 1968; MacMahon, 1971). Of the 13- and 16-month-old baby girls reported by Reid *et al.* (1968), the first died suddenly while playing, with no prior evidence of illness. The second was admitted with a history of vomiting, drowsiness, and left hemiplegia after a fall. She was found to have right bundle branch block and supraventricular tachycardia. She was unresponsive to therapy, developed new thrombotic events, and died 3 days after admission. Reid *et al.* (1968) considered the abnormal cells in the myocardium and in the region of the atrioventricular node as a probable reaction to degenerating myocardial fibers. The 13-month-old girl reported by MacMahon (1971) was the seventh child; the preceding sibling had had multiple developmental anomalies, including cardiac disease, and died at 16 months of age. The propositus had been well until 15 hours before admission. Repeated episodes of vomiting and then tachycardia led to hospitalization; ECG showed arrhythmia and a rate of 200/minute. Half an hour after digitalization and starting intravenous fluids, ventricular fibrillation developed. Recurrent episodes were treated by external cardiac massage, defibrillation, and finally adrenalin,

calcium chloride, and isoproterenol. The next day she developed tonic–clonic seizures. She died 62 hours after admission, and at autopsy had many "xanthoma cells" throughout the myocardium, in the subendocardium and in the septum, involving the conducting system. No data were given as to the intervals between the births of the patient and her six siblings, but the multiple anomalies of the immediately preceding baby suggest that the mother might have been nutritionally depleted, possibly of magnesium. Thus, her last infant might also have been low in magnesium stores, and might have had small coronary arterial disease such as has been implicated in conduction tissue disease.

Another baby girl (8½ months old) first developed an episode of paroxysmal atrial tachycardia (PAT) that responded to digitalis about 2 months before her death (Bove and Schwartz, 1973). The PAT recurred 3 days before her death (while she was still on digitalis), and she was treated with direct current shock and pacing, to which she was unresponsive, developing profound hypotension necessitating administration of epinephrine and isoproterenol. Necropsy examination showed microfoci of acute ischemic necrosis and cells resembling storage histiocytes, containing lipid, scattered throughout the left ventricular wall, the interventricular septum, and both atria. Ultramicroscopy showed mitochondria, many of which were swollen and contained amorphous dense inclusions. In focal areas the cristae were stacked; the outer membranes of adjacent mitochondria were fused to form electron-dense segments. There were focal aggregates of swollen lipid-laden myocardial fibers and myofibrillar membrane-limited dense granular that seemed to be spatially related to early Z-band degeneration. These findings resemble those described under magnesium deficiency. Possibly, the lipid accumulation in this and the preceding case might have been contributed to by the catecholamines given in an effort to correct the hypotension. It is conceivable that the refractory hypotension of these infants might have been the result of magnesium depletion; in magnesium deficiency, *in vitro,* arterial smooth muscle exhibits markedly diminished arterial contraction in response to vasoactive amines (pages 179–183).

8.1.3. Alcoholic Cardiomyopathy and Magnesium Deficiency

Alcoholic cardiomyopathy has been considered a nutritional disease, caused predominantly by thiamine deficiency and by deficiencies of other vitamins (Blankenhorn, 1945). There was then a shift in emphasis, implicating a directly cardiotoxic effect of alcohol, since thiamine is not therapeutic in a substantial number of chronic consumers of hard liquor, and many of the patients are well nourished and respond to prolonged bed rest and abstinence from alcohol (Burch and DePasquale, 1969). More recent work focuses attention on the nutritional aspect of the disease, but this time with the major emphasis on magnesium deficiency as a common denominator in the failure to respond to thiamine, in the arrhythmias seen in alcoholic cardiomyopathy, and in the cardiac lipid accumulation and ultramicroscopic changes.

Thiamine loses enzymatic activity in magnesium-deficient rats, which exhibit signs of thiamine deficiency unless magnesium is repleted (Zieve *et al.* 1968a,b; Zieve, 1969). Furthermore, thiamine levels have been shown to fall in liver and

kidneys of magnesium-deficient rats (Itokawa *et al.*, 1974c). Magnesium-deficient alcoholics are unresponsive to vitamin B_1 (and other B vitamins) until their magnesium is repleted (Zieve, 1975). Magnesium deficiency has long been recognized in alcoholism (Flink *et al.*, 1954; Review: Flink, 1976/1980); it can be secondary to low intake, malabsorption, and, if cirrhosis develops, secondary aldosteronism (Review: Massry and Coburn, 1973). The dependence of thiamine activity on magnesium as a co-factor is relevant (not only to the psychoneurologic manifestations of alcohol withdrawal) but to at least three of the metabolic aberrations that affect the heart in alcoholism.

1. Itokawa *et al.* (1973) have found that there is increased lipogenesis, both in magnesium-deficient and in thiamine-deficient rats. They demonstrated increased lipid and cholesterol in liver and kidneys and hypothesize that these deficiencies lead to a general increase in lipid synthesis, possibly by blocking the pathway of acetate to the tricarboxylic cycle, shunting the acetate to the lipogenesis pathway. Thus, it is possible that the magnesium–thiamine deficiencies are contributory to the accumulation of myocardial lipid droplets that have long been recognized as characteristic of alcoholic cardiomyopathy. Thiamine deficiency has also been shown to cause myocardial catecholamine accumulation (Raab and Supplee, 1944), an effect also demonstrated for magnesium deficiency.

2. Another metabolic aberration to which magnesium–thiamine deficiency might contribute is acetaldehyde accumulation, which might result from blockage of the thiamine-dependent step by which acetaldehyde goes to pyruvate (Altman and Dittmer, 1968). Discussed elsewhere in this volume is the acetaldehyde-induced arrhythmia (which has been shown to be protected against by β-adrenergic blockade), suggesting that it is mediated by catecholamine release, but that might just as well be mediated, in alcoholism, by magnesium deficiency. Contributory to the presumed increased catecholamine effect might be ethanol's interference with catecholamine metabolism (V. Davis *et al.*, 1967b).

3. There is an interrelationship between magnesium deficiency and thiamine (excess) that bears on serotonin levels and metabolism (Itokawa *et al.*, 1972b). Magnesium (as the EGTA chelate) inhibits the release of serotonin from platelets (Henson, 1969). Magnesium deficiency, particularly in the presence of excess thiamine, inhibits the oxidation of serotonin (Itokawa *et al.*, 1974a). Whether ethanol's interference with serotonin's metabolism (V. Davis *et al.*, 1967a) might be intensified by magnesium deficiency and thiamine therapy might be worth investigating.

Further inferential evidence that magnesium deficiency is contributory to alcoholic cardiomyopathy derives from study of the cardiac lesions. (Heggtveit 1965a), who had observed that the coronary arterioles of magnesium-deficient rats were edematous, also observed that intravenous infusion of 20% ethanol into rats caused significant swelling of the capillary endothelial cells (Heggtveit and Nadkarni, 1971).

Pintar *et al.* (1965) reported edema and disorganization of the layers of the coronary arterioles, with perivascular foci of edema, necrosis, and spotty calcification in the hearts of three alcoholic men, 53 to 63 years of age. One also had subendocardial fibrosis. Their aortas and major branches of their coronary arteries showed only minimal atheromatous changes. Alcoholics who died with early stages

of cardiomyopathy were reported to have edema of the coronary vessels (Benchimol and Schlesinger, 1953). Three patients with advanced alcoholic cardiomyopathy, who had died after developing clear signs of acute transmural infarction, had no coronary obstruction but had periarterial myocardial fibrosis (Regan *et al.*, 1975). These investigators speculated that the fibrosis around the myocardial coronary arteries might have interfered with their ability to dilate, thereby causing confluent necrosis when oxygen requirements increased.

Pintar *et al.* (1965) suggested that the vessel wall edema of their alcoholic cardiomyopathic patients might have resulted from hypomagnesemia. Recently, Hungerford and Bernick (1976/1980) gave histologic details of the coronary arterial structural disorganization caused by magnesium deficiency.

Ultramicroscopic studies of alcoholic cardiomyopathic hearts and hearts from magnesium-deficient animals also show similarities. Heggtveit and Nadkarni (1971) reported significant swelling of the mitochondria and sarcoplasmic reticulum after an acute ethanol load in rats, but were unable to induce cardiomyopathy by long-term alcohol feeding. Szanto *et al.* (1967) however, did find some changes in the mitochondria and sarcoplasmic reticulum of alcohol-fed rats. Mice seem to be more susceptible to alcohol cardiomyopathy. Sohal and Burch (1969) found strikingly separated intercalated discs of mice given water containing 15% ethanol for three weeks. Burch *et al.* (1971) then reported that alcohol (ethanol, beer, or wine) produced myocardial damage in mice even when they are otherwise properly fed. The mice developed swelling of the mitochondrial cristae and of the sarcoplasmic reticulum, disorientation of the myofibrils, expansion of the intercalated disc, and accumulation of fatty deposits and dense particles. These changes are very like those reported by Hibbs *et al.* (1965) in six autopsied cases of alcoholic cardiomyopathy: severe mitochondrial swelling, degeneration and fragmentation of the cristae, and formation of dense inclusions. There was also pronounced swelling of the sarcoplasmic reticulum, excessive lipid accumulation, and myofibrillar degeneration and lysis.

Needle biopsy specimens from patients with alcoholic cardiomyopathy also showed severe mitochondrial changes, with subsequent derangement and fragmentation of contractile elements (Alexander, 1966b). This investigator commented that the ultramicroscopic changes resemble those of magnesium-deficient animals, and suggested that the myocardial lesions might be secondary to ethanol-induced magnesium deficiency, rather than a direct consequence of the alcohol *per se*. He referred to the evidence that the metabolism of the vasoactive amines, catecholamine and serotonin, is interfered with by ethanol, and considered the possibility that their accumulation in cardiovascular tissue of alcoholics might thereby be enhanced.

Myocardial biopsy specimens from eight patients with alcoholic cardiomyopathy, and from twelve with idiopathic cardiomyopathy were compared by Bulloch *et al.* (1972). The major ultrastructural lesion in both was contractile element-sarcoplasmic reticulum disorganization. Swelling of the sarcoplasmic reticulum was early and generalized in the alcoholic cardiac disease; it was focal and inconstant in idiopathic cardiomyopathy. In this series of cases, mitochondrial damage was not a major lesion in either diseases.

The similarity of the ultramicroscopic findings in these two diseases of such diverse etiologies, and their similarities to the changes of magnesium deficiency and of a variety of experimental models characterized by loss of myocardial magnesium, suggest that testing for tissue losses of magnesium, and trial of magnesium supplementation be investigated.

8.1.4. Diabetic Cardiomyopathy

Diabetes mellitus is one of the diseases that was first recognized to be associated with magnesium deficiency (Martin and Wertman 1947; Martin *et al.*, 1952, 1958; Martin, 1969, Jackson and Meier, 1968). Additionally, diabetics commonly have diffuse endarterial proliferative small vessel disease (Ditzel, 1954) that resembles the arteriolar lesions of magnesium deficiency. In a study of small vessel disease of the diabetic heart, Rubler *et al.*, (1972) presented cases with fibrosis throughout the myocardium, in conjunction with the damaged intramural vessels. Among 73 patients with "idiopathic" primary cardiac disease, studied by Hamby *et al.*, (1974) 16 had diabetes mellitus, a high frequency of diabetes that was statistically significant. Autopsies were performed in 3 of the 4 diabetic patients with cardiomyopathy who died; all 3 had small coronary, but not large coronary artery disease. In this series of cases, only one of 28 patients with cardiomyopathy without diabetes mellitus had small coronary vessel disease.

T. James (1967) suggested that arrhythmias of diabetes mellitus might be caused by small coronary arterial disease of the vessels supplying the conducting tissue of the heart. Impaired atrioventricular conduction has been found significantly more frequently in patients with diabetes mellitus or abnormal glucose levels (Rubler *et al.*, 1975) than in patients with other diseases.

9
Magnesium Deficiency and Cardiac Dysrhythmia

9.1. Electrocardiographic Changes of Experimental Magnesium Deficiency

In the early subacute magnesium-deficiency study of Kruse *et al.* (1932), convulsions were produced in 86% of the rats by the 18th day, with death occurring after one or more convulsions in 93%. Tachycardia was manifest during the preconvulsive period, and bradycardia with marked arrhythmia just before the convulsions started. Greenberg and Tufts (1938) confirmed these findings, and showed additionally that ECGs, taken while the rats were unconscious from the convulsive seizures, revealed a sinoauricular block, with occasional skipped and ventricular beats. Of 10 rats with less severe magnesium deficiency, such that despite manifest nervousness only one developed convulsions, seven survived long enough to have ECGs recorded the day before sacrifice on day 62. These rats exhibited little change in heart rates (which were slightly slower than were those of control rats on the same diet to which magnesium had been added) but had lengthened P-R intervals. Five of the seven surviving deficient rats had additional ECG abnormalities: Three had numerous extrasystoles, two had abnormally high takeoff of the ST segment in lead III, one with partial heart block and one with auricular extrasystoles.

Production of magnesium deficiency (average serum magnesium = 0.4 mEq/liter) in young dogs, with a diet similar to that used by Kruse *et al.* (1932), produced no significant difference from control heart rate (Syllm-Rapoport *et al.*, 1962). There was a highly significant shortening of the atrioventricular conduction time (P-Q interval) and of the intraventricular conduction time (QRS in Lead II). There was some prolongation of the electrical systole (QT interval). There was an increased incidence of negative T waves in leads I,II, and III that was statistically significant in lead III. The voltage of the negative T waves in leads I, II, and III was statistically significant in lead III. The voltage of the negative T waves in leads I and II was almost half that of controls. Striking inversion of the T waves was

seen in several of the deficient animals. Comparably severe magnesium deficiency, produced with a semisynthetic diet, and that produced severe hypomagnesemia (< 0.5 mEq/liter), but no significant effect on serum potassium or calcium), and that caused arterial and multifocal myocardial lesions, was also associated with ECG abnormalities (Wener *et al.*, 1964). These dogs developed sinus tachycardia, but little difference from control PR, QT, or QRS intervals. There was frequent occurrence, as in the previous group of dogs, of T-wave abnormalities: flattened or inverted T waves, especially in leads III, aVL, and V. They also had consistent RST-segment depression.

Subacute magnesium deficiency for three months in puppies that resulted in irritability and occasional convulsions also resulted in marked sinus tachycardia, peaking of the T waves, and ST-segment depression (Vitale *et al.*, 1961). These dogs also became more susceptible to digitalis toxicity. These investigators pointed out the relationship of these ECG changes to the magnesium-induced shift in potassium. Although the magnesium-deficient dogs also developed hypokalemia, Vitale *et al.* (1961) referred to the loss of intracellular potassium that results from magnesium-deficient interference with mitochondrial enzymatic activity. They speculated that there might be a relatively greater decrease in intracellular than plasma potassium with a relative hyperkalemia. In support of this premise, was the peaked T wave of their magnesium-deficient dogs that resembled that seen in hyperkalemia. Ono (1962) confirmed these findings with young dogs maintained for four months on the same diet as used by Vitale and his co-workers (1961). He, too, found peaking of the T waves, especailly in lead VR, when the serum magnesium levels decreased to 0.7 mEq/liter, with concomitant falls in serum potassium. Depression of the ST segment in limb or chest lead appeared with serum magnesium levels below 0.8 mEq/liter. The P-R interval increased slightly as the hypokalemia worsened. The Q-T interval remained almost normal. There were also occasional premature contractions. Comparable changes were produced by magnesium deficiency in monkeys (Vitale *et al.*, 1963), except for bradycardia and elevated ST segment in severely deficient monkeys. The peaking of the T waves and the ST segment changes were comparable to those seen in hyperkalemia, even though the animals had hypokalemia. This group then tested their original postulate that there might be a local relative hyperkalemia (of the extracellular/intracellular potassium concentration) in the magnesium-deficient heart (Seta *et al.*, 1965, 1966). Rats fed diets low in both magnesium and potassium had substantial reductions in myocardial potassium and magnesium levels. Rats on a low magnesium, adequate potassium intake had almost normal serum potassium level, but markedly subnormal myocardial potassium (Seta *et al.*, 1965), supporting the premise that the hyperkalemia-like ECG of relatively early magnesium deficiency reflects local relative hyperkalemia. Electrocardiographic changes were observed at two-week intervals: T-wave peaking developed within two weeks of instituting the magnesium-deficient diet (best seen in the left precordial unipolar lead). QRS widening and tachycardia were additional early changes (Seta *et al.*, 1966). ST segment depression, ventricular premature beats, and bigeminal rhythm were also seen in some of the dogs. The ECG changes of dogs deficient in both magnesium and potassium resembled those of potassium deficiency, but the terminal T-wave inversion was more marked. The P-

R interval and the QRS segment were prolonged, and there was slight ST-segment depression. The heart rate, unlike that of the animals that were deficient in magnesium but not in potassium, did not change. Dogs that were kept on the magnesium-deficient diet for nine months developed an ECG pattern indistinguishable from that of doubly deficient dogs after two months (Seta *et al.*, 1966).

Electrocardiographic changes, like those of subacute experimental magnesium deficiency, have been reported from studies of cattle pastured on land low in available magnesium (Willers *et al.*, 1965). The ECG criteria for detection of the disease termed "bovine arteriosclerosis" are tented T waves, prolonged QRS interval, and elevated ST segments. The investigators noted that such events in man are associated with hyperkalemia, endocardial thickening, and conduction system-interference. Autopsy reports (of cattle from the herd tested electrocardiographically) showed that endocardial thickening and coronary calcific arteriosclerosis were characteristic (Lynd *et al.*, 1965). Larvor *et al.* (1964a) found that magnesium-deficient calves had tachycardia and shortened PQ intervals. One calf that developed myocardial degenerative changes had had a diphastic T wave. Reference to the conduction disturbance recalls the early microscopic study of magnesium-deficient calves that showed not only endocardial plaques and fibroelastosis and myocardial necrosis, but lesions of the Purkinje fibers (Moore *et al.*, 1936; 1938; Arnold and Fincham, 1950). It also recalls the evidence that the interventricular septum has the greatest avidity for magnesium (Glaser and Brant, 1959; Glaser and Gibbs, 1962; Lazzara *et al.*, 1963; Burch *et al.*, 1965). Thus, the dysrhythmias of magnesium deficiency probably reflect high magnesium requirements of the conduction system, and secondary potassium shifts out of the myocardial cells.

Acute sudden magnesium depletion by hemodialysis has not produced as significant ECG alterations as have subacute or chronic deficiencies. Danzig and Walker (1955) depleted dogs of magnesium over a six-hour period by dialysis, using a magnesium-free, but otherwise physiologically constituted dialysate. The ECGs at the end of dialysis, when the plasma magnesium was 0.34–0.70 mEq/liter showed only an increased heart rate and decreased QT interval. Comparable reduction in plasma magnesium during dialysis for 2½ hours caused only 15% increase in rate and slight decrease in PR and QT intervals (Grantham *et al.*, 1960).

Baby pigs, on a synthetic milk diet that was severely deficient in magnesium, developed bradycardia, increased R and T wave potentials, and inverted T waves in the standard leads (Miller *et al.*, 1964a). Moderate magnesium deficiency resulted in tachycardia with a normal R-wave potential. Acute calcium deficiency also produced bradycardia, with a lengthened ST interval.

Bajpai *et al.* (1978) have correlated the ECG changes produced by hypomagnesemia in rats with abnormalities in mitochondrial oxidative phosphorylation. They confirmed the significant reduction of the P-, QRS-, and T-wave voltages of magnesium deficiency, and attributed the changes to decreased energy production associated with the decreased oxidative phosphorylation. They propose that magnesium deficiency reduces the amount of current transmitted from cell to cell, as a result of increased resistance in the intercellular connections (desmosomes) as these membrane structures swell [similarly to the swelling of the plasma membranes of magnesium deficient erythrocytes (Elin, 1978)].

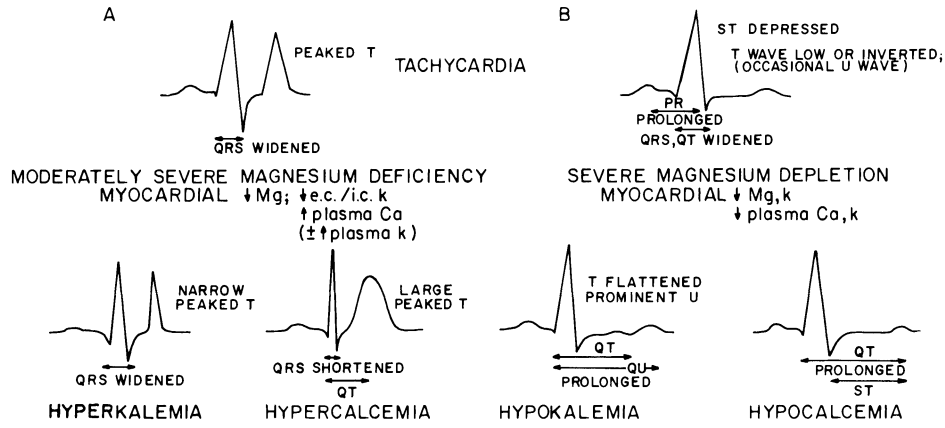

FIGURE 9-1. Schematic representations of electrocardiograms of moderate and severe hypomagnesemia, compared to those of hyper- and hypokalemia and -calcemia. (From Seelig, 1969.)

It might be that the severe forms of magnesium deficiency that are associated with bradycardia and depressed, prolonged ST segments might reflect concomitant hypocalcemia and hypokalemia (Fig 9-1B; Seelig 1969a). The ECG, of the less severe, subacute, or chronic magnesium deficiencies resemble not only that of hyperkalemia but also that of hypercalcemia, or a combination thereof (Fig. 9-1A). Thus, the magnesium-deficiency ECGs reflect also the concomitant or resultant abnormalities of the other two cations that affect the cardiac conduction system, and not the magnesium status alone.

It is provocative that the ECG of magnesium deficiency also resembles that seen in myocardial ischemia of coronary insufficiency: flattened, inverted, or peaked T waves and ST depression, as well as abnormally long QT interval. Its ST depression and T-wave inversion also resemble the ECG of subendocardial infarction, an interesting point, since the small intramural coronaries have been shown to be most compromised in magnesium-deficient animals, and the subendocardial area is most susceptible to ischemia under such circumstances. The presence of endocardial fibroelastosis in infants with perinatal factors that increase the risk of hypomagnesemia is further suggestive evidence that magnesium deficiency might be contributory to the infantile cardiovascular diseases discussed earlier, and that its loss from the heart might be a factor in the ischemic ECG.

9.2. *Magnesium Interrelations with Other Factors in Cardiac Rhythmicity*

Basic to the role of magnesium in maintaining or restoring normal cardiac rhythmicity and in preventing hyperexcitability is its role in maintaining intracellular accumulation of potassium against a concentration gradient, and in counteracting excess calcium influx.

9.2.1. Magnesium/Potassium in Cardiac Rhythmicity

DeCarvalho (1965) has reviewed the factors controlling electrical activity in heart muscle, which is strongly dependent on the electrolyte balance between the cell and its environment. Potassium ions are particularly important in the genesis of cardiac transmembrane potentials, and affect the cardiac rate, impulse conduction, excitability threshold and refractoriness. He considered the influence of alterations in extracellular potassium concentrations on the polarity of the myocardial cell and on transmission of impulses in the special conducting system of the heart. High concentrations of extracellular potassium depress impulse propagation in the atrium and in the His-Purkinje system; low extracellular concentrations depress the atrioventricular (A-V) nodal area, A-V block ensuing with very low (1.5 mM) extracellular potassium levels. Under normal circumstances, potassium is extruded from the myocardial cell during systole. Its return during diastole is an energy-dependent process, since it entails transport against a concentration gradient (Raab, 1969).

The active transport of potassium into, and sodium out of the myocardial cell is dependent on the integrity of the mitochondrial enzyme system. Baltscheffsky (1956, 1957) first postulated that magnesium plays a specific role in the respiratory control of the mitochondrion, since it is a cofactor in the oxidative phosphorylation reactions. Without magnesium, the respiratory rate decreases: there is "uncoupling" of oxidative phosphorylation. He also suggested that magnesium is essential to mitochondrial integrity. A. Schwartz (1971/1972) diagrammed the structure and functions of the mitochondrion which contain magnesium-dependent enzyme systems of the Krebs cycle (and provide most of the energy requirements, as well as those controlling oxidative phosphorylation). Lehninger (1962) showed that the mitochondrial functions are responsible for electrolyte and water transport. Aikawa (1965) reviewed the data on the enzymatic importance of mitochondria and hypothesized that magnesium is essential for the metabolic activity of all subcellular particles. He speculated that there might be an "unknown carrier moleucle" that might be involved in the active transport of the magnesium ion across the inner membrane of the mitochondrion, such as has been identified in cardiac mitochondria (Blondin, 1975; Green *et al.*, 1975).

The importance of oxidative phosphorylation, particularly in Mg-activated membrane ATPase (that is vital in electrolyte transport), was first shown in noncardiac tissue such as nerves, brain, kidney, and erythrocyte membranes (Skou, 1957, 1960, 1962; Post *et al.*, 1960; Dunham and Glynn, 1961; Whang and Welt, 1963; Welt and Tostesen, 1964; Welt, 1964), and in cardiac and other mitochondria and microsomes (Nakamura *et al.*, 1961; DiGiorgio *et al.*, 1962; Auditore, 1962; Auditore and Murray, 1963; Vitale *et al.*, 1963; Schwartz, 1962; Schwartz and Laseter, 1964).

The loss of myocardial potassium in magnesium-deficient animals was first attributed by Vitale and his colleagues (1975a,b) to the uncoupling of oxidative phosphorylation. The myocardial cells (which are vulnerable to magnesium loss because of the high percentage exchangeability of their magnesium, not only lose the capacity to accumulate potassium against a concentration gradient and pump out sodium, but show concomitant mitochondrial disorganization, a not surprising

correlation in view of the dependence on the integrity of the mitochondrial enzymes systems for active electrolyte transport.

9.2.2. *Catecholamine/Magnesium/Potassium Interrelationships*

Epinephrine, whether injected (W. Robertson and Peyser, 1951) or secreted as a result of stress (Raab *et al.*, 1968), causes a decrease in the intracellular potassium/sodium ratio. Using the potent β-adrenegic agonist (isoproterenol), Lehr *et al.* (1966) showed that the earliest myocardial electrolyte changes were significant decreases in magnesium and phosphorus and an increase in calcium. These changes were noted at 3 hours after injection of the catecholamine, in association with mild microscopic evidence of necrosis, but no significant changes in potassium or sodium. There was a significant rise in myocardial sodium and a minor fall in myocardial potassium at 12 hours, at which time the abnormalities in magnesium, calcium, and phosphorus were greater and all of the rats had severe myocardial necrosis.

These observations may help to explain the marked similarity of the ECG produced by excessive sympathomimetic substances (Raab, 1943b) and those produced by nutritional magnesium depletion, whether produced in the experimental animal or as a result of chronic alcoholism or protein calorie malnutrition (Seelig, 1969a). In both there can be elevation or depression of the ST segment, abnormalities of the T wave, ranging from a high pointed shape to inversion and prolongation of the QRS or QT interval. Raab (1943b) pointed out that the epinephrine–ECG pattern reflects the relative hypoxia produced as oxygen consumption exceeds oxygen supply. It is of interest that chronic magnesium deficiency has been shown to cause luminal narrowing of intramyocardial coronary arteries and also to interfere with normal mitochondrial respiration (*supra vide*).

The DOCA saline pretreated rats that showed myocardial magnesium depletion and that died of ventricular fibrillation 15 to 30 minutes after minimal doses (60–100 μg/kg) of isoproterenol, developed auricular and ventricular arrhythmias, progressing to fibrillation as the β-agonist dosage was raised. Epinephrine, as α- and β-agonist, elicited arrhythmias and ventricular fibrillation less consistently, and only when α-adrenergic receptors were blocked (Guideri *et al.*, 1974).

It is surprising that the ECG changes and myocardial damage produced in rabbits stressed by being kept in a vertical position were significantly protected against by oral administration of magnesium chloride (1 g/kg) twice daily, whereas those injected with epinephrine (0.2 mg/kg) intravenously were not similarly protected by $MgCl_2$ (Pokk, 1971/1973). The catecholamine-injected rabbits had been given an unspecified amount of the magnesium every five days before the injection and thereafter. Perhaps the amount given was insufficient to achieve the amelioration of ECG and myocardial changes that was seen in the stressed, magnesium-dosed rabbits. The ECG changes included bradycardia, large R waves, and depressed ST segments.

9.2.3. *Postinfarction/Catecholamine/Free Fatty Acid/Magnesium Interrelationships with Arrhythmia*

It has been shown that blood and urine catecholamine levels are increased in patients who are severely ill after a heart attack and the catecholamines have been implicated in the postinfarction arrhythmias (Gazes *et al.*, 1959; Richardson *et al.*, 1960; Valori *et al.*, 1967; McDonald *et al.*, 1969; Editorial, *Lancet*, 1969a). High levels of circulating free fatty acids have also been implicated in postinfarction arrhythmias (Kurien and Oliver, 1966; Kurien *et al.*, 1969, 1971), and the two findings have been correlated by some, in view of the catecholamines' lipolytic effects (McDonald *et al.*, 1969; Editorial, *Lancet*, 1969b).

When corn oil was added to the diet of sodium phosphate mineralocorticoid-treated (ESCN) rat, it developed infarctlike myocardial lesions and electrocardiographic abnormalities that were similar to those produced by magnesium deficiency in association with local relative hyperkalemia (Vitale *et al.*, 1961, 1963; Seta *et al.*, 1966): There was prolongation of the PR and QRS segments, low voltage, and peaking of the T wave, with atrial fibrillation and conduction abnormalities that developed at about the time that necrosis became visible (Varga *et al.*, 1970). Amiloride protected against the severe ECG changes, but tachycardia persisted and the amplitude of the PR and S waves remained elevated. Cardiac necrosis was almost completely prevented. Serum and myocardial electrolyte analyses of rats sacrificed on the fifth day of study suggest that in this model, the amiloride protection might have been mediated by protection against myocardial necrosis closely resembling those of his electrolyte-steroid cardiac-necrosis (ESCN) experimental model in that all produce extensive, usually multifocal myocardial necrosis. Excessive concentrations of epinephrinelike substance in the heart of a young athlete who had died suddenly (Raab, 1943a), and in hearts of patients who had died with angina pectoris and other cardiac dysfunctions (Raab, 1943b), and the similarity of the ECG changes of patients with IHD to those of animals or humans given epinephrine, led Raab to consider stress-induced hormonal (catecholamine and corticosteroid) excess as basic to the disorder he termed cardiac "dysionism." He observed that major shifts in myocardial electrolytes can lead to disturbances in cardiac rhythm, contractility, structure, and ultimately to cell necrosis. His emphasis was on the depletion of intracellular potassium, but he observed that this was usually paralleled by loss of glycogen and magnesium and by entry of sodium into the myocardial cells.

When cardiac function is inadequate for the load capacity of the heart, relative ischemia develops, which can be manifested by angina, sudden death from arrhythmia, or congestive failure. Hochrein and Lossnitzer (1969) have pointed out that when there is hypoxic cardiac dysfunction or failure, the myocardial metabolism is characterized by shift toward anaerobic from aerobic metabolism, with loss of magnesium and potassium and gain of sodium chloride and water (Fig. 9-2A), with resultant myocardial edema and decreased energy production for the amount of oxygen consumed. A similar pattern results from cardiac overload, except that there is first increased lactate consumption with intensified glycolysis, and subse-

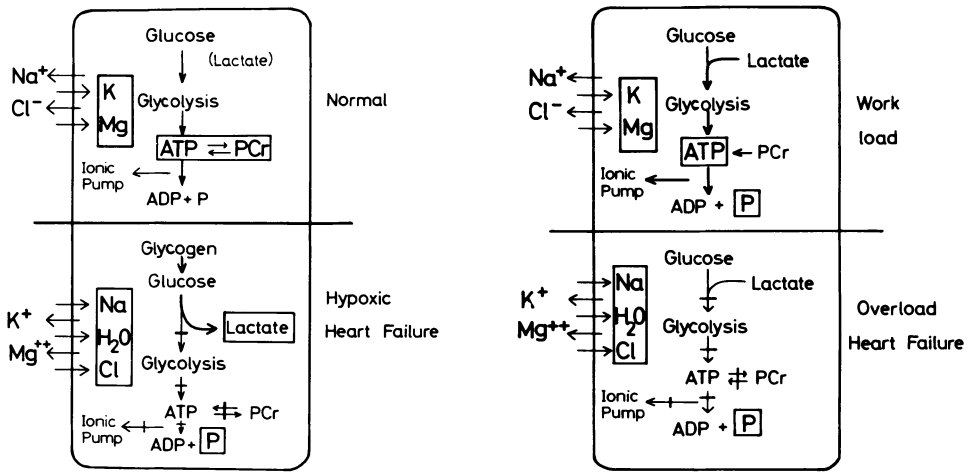

FIGURE 9-2. (A) Effect of oxygen deficiency on the metabolism of electrolytes in the myocardial cell. (B) Effect of overload on the metabolism of electrolytes in the myocardial cell. (From H Hochrein and K Lossnitzer: *Ann NY Acad Sci* 156:387–395, 1969.)

quent inhibition of glycolytic metabolism, again with loss of myocardial magnesium and potassium (Fig. 9-2B).

On the other hand, anoxia itself causes loss of magnesium from the myocardium, as well as increased myocardial lipid accumulation (Review, Opie, 1968), which can further decrease the available magnesium. Even venous occlusion of the arm with a blood pressure cuff causes egress of magnesium from the cells, as reflected by immediate rise in local serum magnesium levels (Whang and Wagner, 1966; Nielsen, 1969). Thus, the similarities between the ECGs of coronary insufficiency and of magnesium deficiency are not surprising. The changes that occur with treatment of the cardiac disease, particularly that increase myocardial calcium and decrease myocardial magnesium (i.e., cardiotonics) and that intensify potassium loss (i.e., diuretics), to which magnesium deficiency contributes (Review: Seelig, 1972) can account for the wide variety of ECG changes seen with cardiac ischemia and decompensation and at different stages of magnesium deficiency.

9.2.4. Blood Primes for Extracorporeal Circulation

The use of acid citrate dextrose (ACD) solution for preserving blood without coagulation is known to remove ionized calcium, and thus calcium is usually added. However, its equal binding capacity for magnesium has not been as widely appreciated, with resultant production of arrhythmias during exchange transfusion in infancy and in open-heart surgery. Killen *et al.* (1971) have shown that total and ionized magnesium levels dropped to below 1.5 mEq/liter and to about 0.5 mEq/liter, respectively, within two hours of the infusion in dogs. Heparin has been recommended as an anticoagulant, to avoid this problem, but Romero *et al.* (1973) performed cardiopulmonary bypass using heparinized blood in dogs, and found a drop of serum magnesium from a pre-bypass level of 1.6 to 1.2 mEq/liter, which

was sustained for the two hours of the bypass and for the hour of observation thereafter. Thus, to avoid the arrhythmias of exchange transfusion and of open-heart surgery, addition of magnesium to the prime is recommended. That the optimal magnesium concentration in the infusate or blood prime might be considerably higher than the physiological concentration, as suggested by the few who have written reports recommending the clinical use of magnesium during open-heart surgery, is indicated by the study of Hearse *et al.* (1978). Using a rat heart model of cardiopulmonary bypass, they showed magnesium to be the single most effective component of any infusate tested. The concentration at which maximal protective activity was achieved was 15 mmol/liter. Increasing the magnesium concentration from 0 to 15 mmol/liter produced a progressive and significant improvement in the recovery of function during the reperfusion. There was a striking increase in protection between 0 and 2.4 mmol/liter and another at 15 mmol/liter; thereafter the protective effect declined with increasing magnesium concentrations (Table 9-1).

9.3. *Magnesium Deficiency in Clinical Arrhythmia*

ECG abnormalities (similar to those seen in magnesium-deficient animals or in animals subjected to stress or given hormonal, drug, and electrolyte challenges that produce loss of myocardial magnesium) have been seen in several clinical conditions that have caused magnesium depletion. Many conditions have been listed as associated with hypokalemic or hypocalcemic ECGs, or both (Surawicz and Lepeschkin, 1953; Judge, 1968; Fletcher *et al.*, 1967; Table 9-2). It is of interest that all of these conditions have been associated with magnesium deficiency: hypomagnesemia, low tissue levels, both, or low tissue levels but high serum levels. Electrocardiograms have been recorded while volunteers were depleted of magnesium. Among the diseases in which abnormal ECGs have been recorded, the most acute situations, those that produce sudden and severe hypomagnesemia, often in association with preceding or concurrent stress, are those during which citrated blood is used. Exchange transfusions of infants, open heart surgery, and extensive surgical procedures or repair of blood loss secondary to serious trauma, are the most

TABLE 9-1. Protective Effect of Magnesium in the Infusate of the Rat Heart Model[a]

Magnesium concentration in infusate (mmol/liter)	Mean % recovery of aortic flow after 30 minutes of perfusion
0	5
2.4	58
4	58
10	60
15	**90**
20	82
30	75
60	50

[a] Derived from Hearse *et al.* (1978).

TABLE 9-2. Conditions with Hypocalcemia ± Hypokalemia and Hypomagnesemia in Which Electrocardiographic Abnormalities Are Seen

Abnormalities	*Diverse treatments with Complications in common*
Gastritis; vomiting	
Diarrhea	Purgation
Ulcerative colitis	
Regional enteritis	Prolonged i.v. fluid
Malabsorption syndromes	Prolonged drainage
Steatorrhea: celiac disease, postoperative	
Protein calorie malnutrition	During correction, refeeding
Diabetes mellitus	During treatment of ketosis
Toxemias of Pregnancy	
Alcoholism	Withdrawal of alcohol
Cirrhosis	Diuretic therapy
Pancreatitis	
Chronic urinary tract infection	During antibiotic therapy (aminoglycosides,
Severe infection	tetracyclines, polyenes)
Hypoparathyroidism	
Metabolic diseases	

obvious examples. The first recognition of the risk of hypomagnesemia and associated arrhythmia in patients receiving long-term intravenous infusions was reported by Flink *et al.* in 1954. The following years this group called attention to the hypomagnesemia of alcohol abuse and diuretic overuse (Flink, 1956; McCollister *et al.*, 1958), both agents that have been associated, as well, with arrhythmias. Infants with "primary" or "idiopathic" myocardial diseases have also been found to have ECG abnormalities resembling those of magnesium deficiency.

9.3.1. Experimental Magnesium Deficiency (Man)

Two normal men were fed diets low in magnesium (1–2.5 mM/day; or 2–5 mEq/day or 25–60 mg/day) and high in calcium for 39 and 48 days, respectively, and were given intravenous infusions of sodium and potassium sulfate to augment renal magnesium loss. One, who developed hypokalemic alkalosis on day 46, developed a hypokalemic ECG, despite a potassium intake of more than 40 mM/day. The plasma potassium rose and the ECG reverted to normal during magnesium repletion (Dunn and Walser, 1966). Seven patients who had had radical head and neck surgery for carcinoma, and thus could be kept on a controlled magnesium-deficient liquid diet for prolonged periods, were more severely depleted of magnesium (Shils, 1969a). Their daily magnesium intakes were 0.5 to 0.8 mEq (60 to 10 mg) for 42 to 266 days. Serial ECGs were obtained on all subjects. Three, who had been depleted for 42, 104, and 117 days, developed changes in the T waves consisting of broadening and decreased amplitude (or occasionally inversion), U waves, and slight prolongation of the QT interval. Two of these patients also had decreased voltage

and one had some shortening of the ST segment. A fourth patient had a prolonged QT interval. These changes were associated with low levels of magnesium, calcium and potassium. Only one patient with severe electrolyte changes had no ECG abnormality. The two patients with the least disturbance in electrolytes had no significant ECG changes. It is noteworthy that during the early period of magnesium repletion, two of the patients' low serum potassium and calcium persisted even though their serum magnesium levels had become normal. Their ECGs remained abnormal until later in magnesium-repletion period, at a time coinciding with restoration of normal serum calcium and potassium levels. Possibly this reflects correction of the ECG when the body stores (including cardiac levels) of magnesium were sufficiently repleted to permit restoration of normal mitochondrial and parathyroid function, without which inability to maintain normal potassium and calcium levels is not surprising, despite their supplementation.

9.3.2. Electrocardiographic Changes with Use of ACD Blood

9.3.2.1. Exchange Transfusion

The evidence that exchange transfusion with ACD blood has produced acute magnesium deficiency in newborn infants has been discussed earlier. The most consistent change associated with a drop in serum ionized magnesium to below 0.8 mEq/liter, was characterized by a flat T wave (Bajpai *et al.*, 1971, 1972). A similar tracing was seen in another infant, who was unsuccessfully treated with calcium gluconate for hypocalcemic seizures, noted first six days after he had undergone an exchange transfusion (Dooling and Stern, 1967). A flat T wave was noted in the third week of life when, despite continuation of calcium therapy and sodium bicarbonate treatment of his acidosis, the baby continued to suffer disastrous seizures, which were finally attributed to his concomitant hypomagnesemia (0.6 mEq/liter), reported first from blood taken on the 11th day of life. His tremulousness and seizures ceased in response to 0.25 ml of 50% magnesium sulfate every six hours (providing 25 mEq in 24 hours), but his serum magnesium remained low (0.76 mEq/liter); it was at this time (three days after the magnesium therapy had been started) that the abnormal ECG was first observed. The infant required 0.5 ml of 50% magnesium sulfate intramuscularly every eight hours to bring his serum magnesium up to 1.6 mEq/liter and to correct the flat T waves. In a short communication, Rosefsky (1972) reported that a premature infant, who had required several exchange transfusions, and who had been given calcium prophylactically, developed arrhythmia with many ectopic ventricular beats during his fourth transfusion. This infant responded to slow intravenous injection of magnesium sulfate (25 to 50 mg/kg) within five minutes, with return of rhythm to normal. When the ectopic beats recurred on subsequent exchange transfusions, intravenous magnesium therapy again rapidly restored the rhythm to normal. ECG changes: high P waves, ST depression, and flat or inverted T waves, are common during exchange transfusions (Robinson and Barrie, 1963). Citrate-lowered ionized magnesium (Bajpai *et al.*, 1967a,b) has been implicated in the high sudden-death rate during this procedure (Editorial, *Canad Med Assoc J*, 1967).

9.3.2.2. Open-Heart Surgery

The use of ACD blood in the pump oxygenator prime during cardiopulmonary bypass (performed during hypothermic or normothermic anoxic arrest with ventricular fibrillation) has been associated with even more arrhythmias. Scheinman *et al.* (1969) investigated the pre- and postoperative magnesium status of 17 adult patients undergoing intracardiac operative procedures, after they had observed classic neuromuscular signs of acute magnesium depletion in a patient soon after cardiopulmonary bypass. Levels of three of the patients could not be compared because they had remained in persistent fibrillation, despite standard therapy (including multiple attempts at internal defibrillation) until they were given an intravenous bolus of magnesium sulfate. Of the remaining 14, 12 exhibited drops in serum magnesium from 1.65 ± 0.10 mEq/liter before surgery to 1.07 ± 0.01 mEq/liter after surgery. Despite the hypomagnesemia, no gross neuromuscular abnormalities were noted. This group of investigators then compared those patients with another group of eight, who had magnesium (2 mEq/liter) added to the pump prime (R. Sullivan *et al.*, 1969; Scheinman *et al.*, 1971/1973). Although there was no apparent relationship between postoperative serum magnesium levels and the development of new postoperative arrhythmias, 9 of the 17 patients in the first group developed such arrhythmias, whereas only 2 of the 8 to whose prime magnesium had been added developed arrhythmias. An average of 6.2 shocks at 4 watts/second was necessary for internal defibrillation in the first group versus 1.3 shocks in the second group. The first group of patients had a 30.3% drop in postoperative serum levels versus a 17.4% drop in the second group. Although the fall in serum magnesium was significantly less in the second than in the first group, five of the eight subjects still became hypomagnesemic. The authors suggested that physiologic amounts of magnesium should thus be added to all administered fluids, as well as to the pump prime, and that the magnesium levels should be monitored in all cardiac surgery patients (Scheinman *et al.*, 1971/1973).

Buky (1970) commented that the fibrillation produced during open-heart surgery is a consequence of induced hypothermia, and occurs at an esophageal temperature of about 27° C. (The nature of the pump prime was not noted.) He found that an intravenous bolus of magnesium sulfate (0.1 g/kg intravenously) facilitated postoperative defibrillation, making electrical shocks unnecessary in 18 (66.7%) of the 27 patients so treated, as compared with only eight (19.5%) of the 41 patients not given the magnesium. Spontaneous defibrillation took place when the magnesium level in the serum reached 4.5–5.0 mEq/liter.

Proof that increasing the magnesium/calcium ratio favorably influences the defibrillation threshold was provided by Koning *et al.* (1971/1973), using dogs on cardiopulmonary bypass. They found that magnesium lowered and calcium increased the pulse amplitude needed for defibrillation. On the basis of their observation, they suggested that it might be useful to administer magnesium to a patient prior to defibrillation.

It has been clearly demonstrated that patients undergoing cardiac surgery lose magnesium, as indicated by increased renal clearance of magnesium despite hypomagnesemia (Scheinman *et al.*, 1969, 1971/1973) and by serum magnesium levels which are markedly lower during and after the surgical procedure and which remain subnormal for three to seven days postoperatively (Holden *et al.*, 1972; Khan *et*

al., 1973). Even on the day of admission the average serum magnesium levels of the prospective open-heart surgery patients were 10% below normal (1.35 mEq/liter); most with low levels had been on diuretics (Holden *et al.*, 1972). At the end of the operation the average serum magnesium level was 20% below normal (1.1 mEq/liter), and the day after surgery it dropped to 30% below normal (1.04 mEq/liter). It gradually rose thereafter to 5.5 and 1% below normal by the seventh postoperative day and discharge day, respectively. As in the initial study of Scheinman *et al.* (1969), this group found no definite relationship between the degree of individual lowering of serum magnesium and problem of postoperative arrhythmia. These investigators commented on the role of the citrate in removing ionized magnesium as well as of calcium, on the high flow perfusion in increasing urinary magnesium loss, and on the sharp drop in serum levels despite increased tissue catabolism and hypoxia, which cause shifts of intracellular to extracellular fluids. That patients undergoing open-heart surgery lose myocardial magnesium in the course of the procedure has been demonstrated by Singh *et al.* (1971/1972). They took myocardial biopsies soon after interruption of coronary flow for about 20 minutes in 16 patients, immediately before reeestablishment of coronary flow in 2 and after coronary reflow in 14. They reported that loss of magnesium and potassium from the myocardium was a constant finding, that of magnesium ranging from 2% to 19%.

Khan *et al.* (1973) gave magnesium supplements to two groups among his 29 open-heart surgery patients: (1) a group of 8 who developed multiple ectopic beats, extrasystoles, and periods of tachycardia postoperatively (100 mg magnesium as the chloride, orally, starting on the third postoperative day), and (2) another group of 8 who were given 100 mg of magnesium (as the chloride) orally pre- and postoperatively and to whose priming fluid 90 mg of magnesium (as the sulfate) was added. In contrast to the magnesium levels of nine adults not given magnesium supplements preoperatively, and who had not had magnesium added to the ACD blood prime, who developed definite hypomagnesemia by the end of the procedure, most of those treated prophylactically became only slightly hypomagnesemic after surgery (Fig. 9-3). Also, those given magnesium showed much more rapid return to normal serum magnesium levels. As a result of these findings, Khan *et al.* (1973) began routine use of 200 to 300 mg of magnesium chloride daily, by mouth, in divided doses, preoperatively, and up to 35 mg of magnesium as the sulfate in each 500 ml of dextrose saline solution postoperatively. In addition, they primed the heart-lung machine with 120 mg of magnesium as the sulfate. This regimen keeps the postoperative serum magnesium levels within normal limits. Caution is exercised in the presence of impaired renal function.

Holden (1978) has recently reported a double-blind study of 70 cardiac surgery patients who were randomly assigned to two postoperative treatment groups: (a) six intravenous doses of 2 ml of a $MgSO_4$ solution containing 0.8 mEq/liter, starting an hour after surgery and thereafter every six hours intramuscularly; and (b) placebo solution of 2 ml normal saline. There was persistent hypomagnesemia for 72 hr postoperatively in the placebo group, and correction of the hypomagnesemia in the group treated with $MgSO_4$ (Fig. 9-4), differences that were significant ($p \leq 0.001$) with high confidence limits (90%). Atrial fibrillation had been present in similar numbers in each group preoperatively. Twelve of the preoperative atrial fibrillating patients treated with placebo continued to fibrillate postoperatively, versus one in the magnesium-treated group (Table 9-3). There were more postoperative clinical

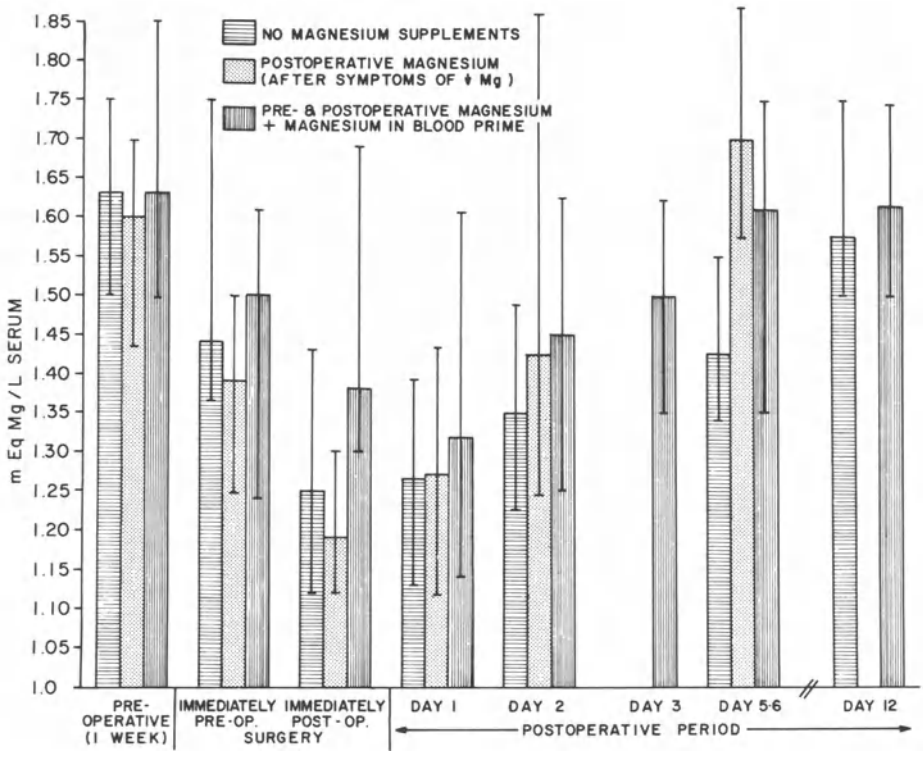

FIGURE 9-3. Serum magnesium in open-heart surgery patients without and with magnesium supplements. (Derived from Khan *et al.*, 1973.)

problems in the group receiving placebo than in those treated with magnesium (Table 9-4). Holden (1978) observed that patients whose plasma magnesium levels were in the normal range were more readily paced than were those whose levels were subnormal. He also commented that, in addition to the patients in his double-blind study, he had encountered 11 (with marginally low mean magnesium level of 1.5 mEq/liter) whose ventricular fibrillation was refractory to conventional treatment for half an hour, and who rapidly responded to intravenous magnesium by return to sinus rhythm or conversion to atrial fibrillation (Table 9-5).

The development of ischemic contracture of the heart—"stone heart"—during open-heart, cardiopulmonary surgery is rare (Cooley *et al.*, 1972). Of 13 patients (among almost 5000 cardiac procedures in one institution), all had advanced cardiac disease. Twelve had interstitial fibrosis; all had severe myocardial hypertrophy, but only 4 had evidence of recent ischemia. The condition has been totally refractory to reversal. Cooley *et al.* (1972) suggest that the tetanic contracture might reflect ATP-depletion, or possibly accumulation of calcium, and that catecholamine production (in response to the ischemia) might intensify the situation. Katz and Tada (1972) considered the biochemical mechanism that might be operative in this surgical catastrophe. They point out that ATP can promote contraction (by causing actin and myosin to interact) or relaxation in the presence of increased magnesium concentration. They speculate that the hypertrophied hearts, which might be subject to

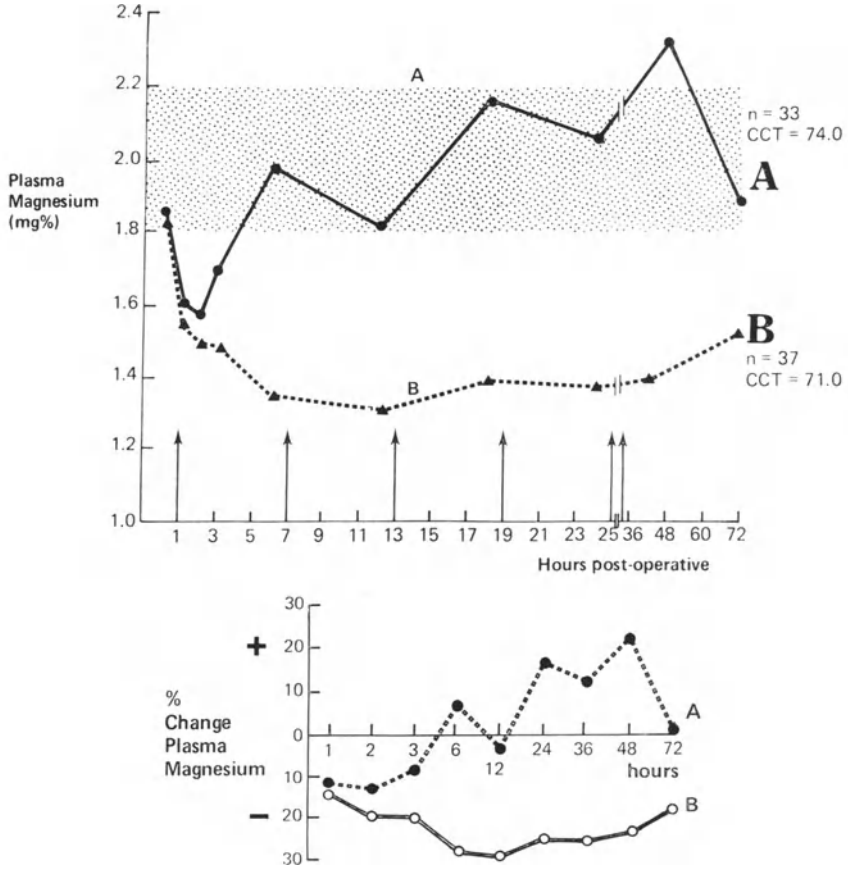

FIGURE 9-4. Plasma magnesium levels in cardiac surgery patients given magnesium (group A) or placebo (group B) postoperatively. CCT: Creatinine Clearance Test. (Courtesy of MP Holden, 1978.)

development of the contracture during surgery, might have been functioning with depleted stores of energy phosphate compounds. Furthermore, such patients are likely to have undergone vigorous diuresis, that leads to metabolic alkalosis (Katz and Tada, 1972), and loss of magnesium (Bajpai *et al.*, 1971/1973; Holden *et al.*, 1972; Lim and Jacob, 1972a; Khan *et al.*, 1973; Loeb *et al.*, 1968; Seller *et al.*, 1966;

TABLE 9-3. Sinus Rhythm versus Atrial Fibrillation in Cardiac Surgery Patients Treated with $MgSo_4$ (Group A) or with Placebo (Group B)[a]

	Preoperative status		Postoperative problems		No Postoperative problems	
	A	B	A	B	A	B
Atrial fibrillation	18	22	1	12	17	10
Sinus rhythm	15	15	1	4	14	19

[a] From Holden (1978).

TABLE 9-4. Incidence of Clinical Problems in Cardiac Surgery Patients Given Magnesium Postoperatively (Group A) and Those Given Placebo (Group B)[a]

Clinical problems	A (33)[b]	B (37)[b]
Pacing difficulties	0 (3)[c]	8 (21%)
Arrhythmias	2 (7)[c]	9 (24%)
Arrhythmias following digoxin	0 (3)[c]	3 (8%)
Mental problems	2	8 (22%)
Peripheral neurological problems	1	4 (11%)
Deaths	2	1 (3%)

[a] From Holden (1978).
[b] Number in parentheses indicates the number of patients.
[c] Number in parentheses indicates the number of patients with problems only in the first hour after surgery.

TABLE 9-5. Response to i.v. Magnesium of Cardiac Surgery Patients with Ventricular Fibrillation Refractory to Conventional Therapy[a]

11 patients:	9 postoperative
	2 preoperative
Mean plasma magnesium during ventricular fibrillation = 1.79 mg/100 ml	
Received:	lignocaine, epanutin, β-blockers
	correction acidosis
	cardiac massage, mean ½ hour
	defibrillation shocks, mean 12
All returned to sinus rhythm or atrial fibrillation within 2 min of i.v. $MgSO_4$ (2 ml 5%) = 0.81 mEq	

[a] From Holden (1978).

Wacker, 1961). and probably also have received cardiac glycoside therapy, which increases myocardial calcium uptake and loss of myocardial magnesium (Holland, 1964). Since "calcium rigor" has been produced in frogs' hearts, suspended in Ringer's solution with an excess of calcium (Fukuda, 1970), it is possible that addition of magnesium to the preoperative regimen and to the pump prime might function to protect against development of "stone heart."

9.3.2.3. Surgery, Drainage, and Magnesium-Free Intravenous Infusions

Prolonged use of magnesium-free parenteral fluids is another cause of acute magnesium depletion that has been associated with arrhythmias, the one that was identified first. Flink *et al.* (1954) described an ECG, characteristic of hypokalemia, in a patient who had received prolonged parenteral therapy, that was associated with hypomagnesemia and that was corrected by intramuscular magnesium sulfate therapy. It was not until five years later that cardiac irritability, responsive to magnesium therapy, began to be noted in the literature as a risk of surgery, prolonged parenteral therapy, and loss of gastrointestinal fluids, whether from drainage, intractable vomiting, or diarrhea. R. E. Randall *et al.* (1959) reported several such patients. One had, in addition to neuropsychiatric manifestations of combined hypomagnesemia and hypocalcemia, developed QT prolongation, and depressions of the ST segments and T-wave voltage after infusion with calcium gluconate. Mag-

nesium sulfate was then added to the intravenous fluids, and 18 hours later all of his manifestations of a "terminal" state had cleared. Similar ECG changes were seen in a 38-year-old diabetic man in the Randall *et al.* (1959) series. This patient had renal wastage of magnesium, and improved somewhat following a 2-week course of parenteral magnesium therapy, only to die of a myocardial infarction a month later. Other patients in this series, whose abnormal ECGs improved with magnesium therapy, had alcoholism or chronic glomerulonephritis. Among the W. O. Smith *et al.* (1960) series of 18 patients with nonalcoholic neuropsychiatric manifestations of magnesium depletion (10 of whom had sinus tachycardia and sometimes frequent premature ventricular systoles) were 3 who had had prolonged infusions, 1 who had long-term severe diarrhea, and 4 with acute pancreatitis. Hanna *et al.* (1960) reported 3 patients with ECG signs of magnesium depletion: low voltage of all complexes, which increased following treatment with magnesium chloride. One of their patients had had malabsorption and had been given very high doses of vitamin D, as had another for renal osteomalacia. The third was hypomagnesemic immediately following parathyroidectomy. Baron (1969) reported a patient who developed magnesium-responsive tachycardia after surgery and prolonged parenteral fluids.

The ECG changes of a patient who had undergone extensive surgery and received intravenous fluids and had gastrointestinal suction following a complicated postoperative course were reported in detail by Kellaway and Ewen (1962). When her serum magnesium level was 1.3 mEq/liter, she exhibited flattened T-wave and ST depression that were apparent particularly in the chest leads, but also in the standard leads (Fig. 9-5). Magnesium sulfate (20%) was added to the i.v. fluid and given at the rate of 8 mEq/hour. Within 24 hours, her ECG had returned to normal (Fig. 9-6). In addition to her moderate hypomagnesemia, this patient had slightly higher than normal plasma potassium (5.7 mEq/liter), but because her ECG was more like the tracings seen in severe hyperkalemia, the authors considered the hypomagnesemia contributory. They suggested that serial electrocardiography might be a helpful adjunct in controlling electrolyte replacement therapy. Five years after the published case report, the patient was seen by Dr. Kellaway, who reported her in good health and with a normal ECG (personal communication).

Thoren (1963), who presented a detailed biochemical and surgical report of 15 patients with magnesium deficiency secondary to losses of gastrointestinal fluids,

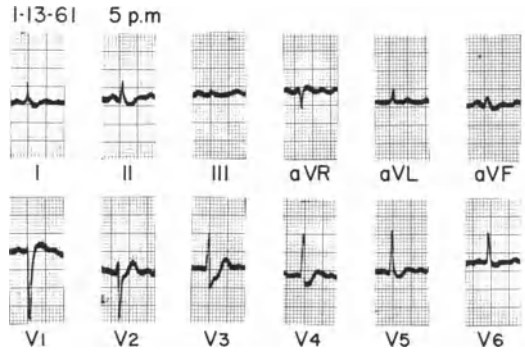

FIGURE 9-5. Electrocardiogram of clinical magnesium deficiency. (From G Kellaway and K Ewen, *New Zeal Med J* 61:137–142, 1962.)

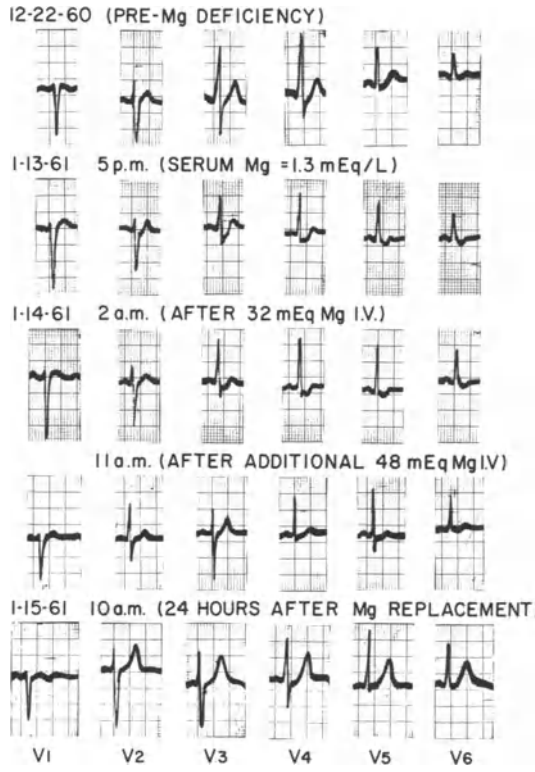

FIGURE 9-6. Electrocardiographic response to magnesium (i.v.) of hypomagnesemia (secondary to abdominal surgery, prolonged gastric suction, and magnesium-free parenteral fluids). (From G Kellaway and K Ewen: *New Zeal Med J* 61:137–142, 1962.)

reported the ECG of only one. That patient (with prolonged biliary drainage) first had an ECG described as typical of hypokalemia, despite ample potassium supplements, and then developed postoperative tachycardia, intraventricular conduction block, and unspecific ST–T changes. W. O. Smith (1963) reported 7 patients with postoperative, neuropsychiatric signs of magnesium deficiency, all but one of whom had been on constant gastric drainage and all of whom had been on magnesium-free intravenous fluids for 1 to 90 days with little or no oral intake. Of this group, whose serum magnesium values ranged from 0.50 to 1.29 mEq/liter, tachycardia, acute hypertension, or both were seen in four. Treatment with magnesium intravenously or intramuscularly, as recommended by Flink (1956), produced marked improvement in all cases within 4 to 24 hours. In a brief case report of a patient with ulcerative colitis, who had a preoperative ECG suggestive of hypokalemia, and who had been intensively treated with blood transfusions, ACTH, oxytetracycline as well as "vigorous" potassium therapy, Matko (1966) mentioned ST–T abnormality and typical neuropsychiatric signs of acute magnesium depletion after a stormy postoperation course, necessitating gastric suction and continuous intravenous feeding. The body magnesium stores of this patient must have been severely lowered, in view of her illness, that was associated with long-term diarrhea, the administration of ACTH and blood (probably citrated), and even the tetracycline, which chelates

and inactivates magnesium (Shils, 1962). Yet her serum magnesium level at the height of her signs of depletion was only moderately low (1.2 mEq/liter). She responded promptly, with subsidence of all of the signs of magnesium depletion, after having had four grams of magnesium sulfate (32.5 mEq magnesium) given intravenously in 250 ml 5% dextrose in water over 2-hour period.

It is not possible to assess the frequency of magnesium-deficiency-induced ECG abnormalities developing in patients who have undergone major surgery and/or had drainage and prolonged parenteral fluids. Henzel *et al.* (1967), who reviewed the risks and consequences of magnesium deficiency in surgical patients, referred to low voltage ECG, tachycardia, and premature ventricular contractions as manifestations that might develop, and cited the special risk of any potential surgical candidate whose abnormal nutritional status might lead to magnesium deficiency. What is needed is a systematic survey of the magnesium status of such patients for ECG abnormalities, and for their response to magnesium therapy, with electrocardiographic monitoring, as recommended by Kellaway and Ewen (1962).

9.3.3. Malabsorption and Magnesium-Deficient Arrhythmias

The literature reviewed has uncovered few patients with malabsorption syndromes, in which electrocardiographic changes have been attributed to magnesium depletion, to which this group of patients is particularly susceptible. However, hypokalemic and hypocalcemia ECGs have been attributed to gastrointestinal disorders that lead to losses of potassium and calcium (Lepeschkin, 1959). It is likely that magnesium depletion participates as well, contributing both to potassium loss (Review; Seelig, 1972) and to hypocalcemia (Review: Massry, 1977). Furthermore, severe hypomagnesemia causes ECG tracings resembling a combination of characteristics seen with potassium and calcium depletion.

The patient reported by Gerst *et al.* (1964), who developed severe hypomagnesemia (0.37 mEq/liter), with confusion, tremors, convulsions, and a sinus tachycardia of 140/minute, had had several segmental bowel resections and long-term loss of intestinal fluids from his stoma. This patient showed clearing of sensorium and tremors, with subsidence of tachycardia within six hours of receiving 4 grams of $MgSO_4$ (40 ml 10% solution of 500 ml of dextrose and water). Bajpai *et al.* (1971/1973) have reported the ECG changes of two patients with severe steatorrhea and

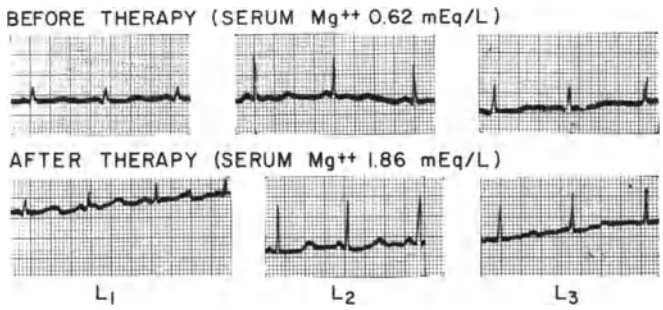

FIGURE 9-7. Electrocardiographic changes in hypomagnesemia (secondary to malabsorption); effect of oral Mg treatment. (From Bajpai *et al.*, 1971/1973.)

malabsorption, who had almost as low serum magnesium levels: 0.62 and 0.82 mEq/liter. They both had tachycardia, low PQRS voltages, and flat to inverted T waves. These patients were given oral magnesium chloride supplements (124 mEq magnesium/day, added to the standard hospital diet) for 21 days. This treatment corrected the hypomagnesemia and resulted in improved PQRS voltage and T waves (Fig. 9-7). Lim and Jacob (1972d) reported low voltage and flat T waves in the ECG of three of seven patients with chronic diarrhea, two of whom had hypomagnesemia (1.4 mEq/liter and 1.1 mEq/liter), but all of whom had subnormal skeletal muscle magnesium levels.

Previously undetected malabsorption and steatorrhea was identified in a 72-year-old woman, who was admitted to the hospital with a history of sudden onset of palpitations and syncope the day before and two hours before admission (Chadda *et al.*, 1973b). She had premature ventricular systoles and minor ST abnormalities. She then developed supraventricular tachycardia, and was found to have hypokalemia (3.0 mEq/liter). Intravenous potassium chloride raised the blood levels to normal, but did not correct the arrhythmia. She was then found to have severe hypomagnesemia (0.35 mEq/liter). During the next paroxysm of supraventricular tachycardia with aberrant conduction, an intravenous injection of 2 ml 25% magnesium sulfate caused prompt return to sinus rhythm. She was then given a constant infusion of 1 g magnesium sulfate (8 mEq Mg) per hour for 12 hours, at which time her serum magnesium level became normal. After diagnosis of malabsorption, she was given oral and intramuscular magnesium supplements for a year and had no recurrence of syncope or cardiac arrhythmia.

The syndrome, protein caloric malnutrition (PCM), is an example of gastroenteritis in babies and young children in which magnesium-responsive ECG changes have developed during the "recovery syndrome." Caddell (1965) reported ECG changes, such as have been reported in severe experimental magnesium deficiency, in PCM children fed high-protein milk with added potassium and sodium chloride. She compared the ECGs of 103 affected children on the standard regimen with and without magnesium supplements. On admisstion, most had sinus tachycardia (130 to 160/min); some had bradycardia. On admission the rate was usually very labile. P waves were small, absent, or notched; the PR interval was short, and there were dwarfed QRS complexes, ST abnormalities and flat or inverted T waves in limb leads I and II and in left precordial leads V_5 and V_6. Intermittent gallop rhythm occurred in four, one of whom developed ventricular ectopic beats the day before death. The children given magnesium supplements usually showed some lengthening of the previously fixed short PR interval, and greater increases in the T-waves amplitude than were seen during the recovery phase of the nonsupplemented children. The improvement of the other complexes was not specifically attributed to the magnesium. In later studies, Caddell (1967, 1969a,b) reaffirmed and extended her observations in the ECG abnormalities of PCM, and their response to magnesium therapy. She found the PCM children with flat or inverted T waves over the precordium on admission generally grew worse on the standard therapy. After five days treatment, there was further inversion of the T waves, development of labile heart rate, and rarely ventricular ectopic beats. These children were usually hypotensive, and tolerated blood transfusions and digitalis poorly. The transfusions often led to congestive heart failure; the digitalis given in the usual therapeutic dose usually led to severe arrhythmias and gastrointestinal disturbances. When magnesium

(0.5 mEq/kg) was given intramuscularly, clinical improvement was noted within six hours. The precordial impulse improved, the cardiac sounds became louder and of better quality, and a stable normal sinus rhythm developed (Caddell, 1969b).

Caddell made an interesting observation that seems worth exploring. She commented that survivors of PCM often have persistent PR interval and T-wave abnormalities, that endomyocardial fibrosis is found in the same geographic regions as PCM, and that the morphology of the cardiac lesions resemble those that Selye (1958f) reported to be protected against by magnesium and potassium. She speculated, thus, that the ECG abnormalities of PCM might reflect mineral imbalance, and that persistent deficiencies of magnesium and potassium might be contributory to the development of endomyocardial fibrosis (Caddell, 1965).

Hypocalcemic ECG tracings were obtained from a baby with isolated magnesium malabsorption that did not respond to calcium but improved once high magnesium requirements were met (Nordio *et al.*, 1971).

9.3.4. Arrhythmias of Starvation

Sustained loss of magnesium from lean tissue and bone has been reported among volunteers (nonobese) who have undergone short- to long-term (45 days) periods of starvation. Keys *et al.* (1950) has reported slight prolongation of the QT interval in volunteers who underwent prolonged starvation, and suggested that this might indicate myocardial damage.

Obese patients who fast to lose weight are at even greater risk, both because they lose substantial amounts of magnesium and because they mobilize body fat, which increases risk of magnesium depletion (Consolazio *et al.*, 1967; Jones *et al.*, 1966; Drenick *et al.*, 1969; Drenick and Brickman, 1971/1973). A dramatic case that had ECG signs suggestive of magnesium deficiency was a twenty-year-old woman who died on the seventh day of refeeding after 30 weeks of starvation, and was found to have cardiomyopathy at autopsy (Garnett *et al.*, 1969). She had normal serum electrolytes except for one episode of hypokalemia, at which time the ECG showed ST depression and slight QT prolongation. She was given potassium supplements, despite which she had further loss of exchangeable potassium (from 3360 mEq to 1400 mEq), indicating loss of lean mass tissue. After her cardiac arrest, which responded to cardiac massage, she had an obviously prolonged QT interval and T-wave inversion in leads I, aVL, and aVR. She was given a slow intravenous potassium infusion, which was stopped when the report of plasma potassium of 3.7 mEq/liter was received. Her serum levels of magnesium and calcium were 2.25 and 8.4. She was then given 1 g of calcium chloride in 5% dextrose in an hour, at which time she developed multifocal ventricular extrasystoles, and lignocaine was substitued for the calcium. She again had an episode of ventricular fibrillation seven hours later, her QT interval remained lengthened despite having received 30 mEq of potassium overnight, and she died of ventricular fibrillation refractory to electrical defibrillation. The authors had considered the possibility of magnesium deficiency, but were reassured by the normal serum magnesium level. Fasting patients have maintained normal or even elevated serum magnesium levels despite sustained loss of magnesium stores (Sunderman, 1947; Sunderman and Rose, 1948). Whether this patient would have survived had she been given magnesium chloride, rather than potassium and calcium, cannot be averred. In view of its cardioprotective effect,

TABLE 9-6. Electrocardiographic Findings in Alcoholic Heart Disease[a]

Data	Percent
Persistent sinus tachycardia	25.2
Arrhythmias	
Atrial fibrilation	18.9
Atrial flutter	2.4
Ventricular tachycardia	0.8
"T-P phenomenon"[b]	22.8
First degree A-V block	7.1
Third degree A-V block	2.4
Left bundle branch block	6.3
Right bundle branch block	3.1
Intraventricular conduction defect	5.5
Nonspecific STT changes	10.2
Notched or tall P waves	4.7
Left ventricular hypertrophy	3.1
Left ventricular strain	7.1
Right ventricular hypertrophy per right ventricular strain	2.4
P pulmonale	10.2
Myocardial infarct pattern	2.3

[a]From Alexander (1968).
[b]Relative S-T prolongation and tachycardia.

however, it is suggested that this approach, possibly with potassium chloride, might be worth trying. Another obese patient, one who had been dieting on a liquid-protein diet supplemented with vitamins, calcium, and potassium, and who developed syncope and arrhythmia, had a low serum magnesium level (1.5 mEq/liter) that was considered marginally normal; she was given a constant infusion of magnesium (dosage not specified). Her serum magnesium level never rose to over 1.67 mEq/liter, and she died of ventricular fibrillation and cardiomyopathy (Michiel *et al.* 1978).

9.3.5. *Arrhythmias of Alcoholism*

Tachycardia and hypokalemia-like ECG changes were observed by Flink and his collaborators (1954, 1957) and by Smith and Hammarsten (1959) in patients with alcohol withdrawal symptoms and signs, which responded to magnesium therapy. It is noteworthy that arrhythmias and ECG changes reported in heart disease of chronic alcoholism are often found in association with hypomagnesemia (Flink *et al.*, 1954, 1957; Randall *et al.*, 1959; Fankushen *et al.*, 1964; Milner and Johnson, 1965; Loeb *et al.*, 1968; Hartel *et al.*, 1969; Ricketts *et al.*, 1969; Bajpai *et al.*, 1971/1973; Iseri *et al.*, 1975; Iseri and Bures, 1976/1979). Alexander (1968), who had noted the similarity of the ultramicroscopic changes seen in alcoholic cardiomyopathy and those seen in magnesium-deficient animals (Alexander, 1966a,b) tabulated the ECG findings in alcoholic heart disease from a series of 127 admissions for 66 patients (Table 9-6). Brigden and Robinson (1964), who had earlier considered it likely that the magnesium loss caused by alcoholism might be contributory to the cardiomyopathy of alcoholism, also referred to the wide range of ECG abnormali-

TABLE 9-7. ECG Findings in 100 Chronic Alcoholics in Finland[a]

		Total material	Age group 40–59
	NUMBER:	100	64 (64%)
	NORMAL:	38	22 (34.4%)
	WITH FINDINGS:	62	42 (65.7%)
Minnesota Code No.			
I	Myocardial infarction	3	2 (3.1%)
IV	ST depression	2	1 (1.6%)
V	Negative or flat T waves	10	5 (7.8%)
II_1	Left axis deviation	1	1 (1.6%)
III	High R waves	7	4 (6.3%)
VII_1	LBBB	2	1 (1.6%)
$VIII_3$	Atrial fibrillation	2	2 (3.1%)
6	Nodal rhythm	1	1 (1.6%)
7	Sinus tachycardia	21	13 (20.2%)
IX_1	Low voltage	4	3 (4.7%)
2	High T waves	8	6 (9.4%)
4	Prolonged QT (> 10%)	7	5 (7.8%)

[a] From Härtel *et al.*: *Acta Med Scand* 185:507–513, 1969.

ties found. Among his 50 patients, who had consumed large quantities of alcohol, tachycardia was present whether or not there was sinus rhythm. Ectopic beats were common and often multifocal. Half had atrial fibrillation at some time; it was more common in the older patients. Abnormalities of the T waves occurred in most of the ECGs. Conduction defects were present in 19 of the patients. The authors noted that the ECG findings are dependent on the site and extent of myocardial damage: A small area of damage strategically placed causes a more significant conduction defect than a similar lesion deep in the muscle mass. U-wave abnormalities, such as are seen in hypokalemia, were reported also in the ECG of a young man with alcoholic heart disease, who had hypomagnesemia (0.75 mEq/liter) but normal potassium serum levels (Ricketts *et al.*, 1969). He also had alternating upright and inverted T waves, and the more common sinus tachycardia. These abnormalities were intermittent and cleared during hospitalization even though he was not given magnesium therapy and received digitalis and diuretics. T-wave alternans was reported in a man with long-lasting heavy drinking, who had hypomagnesemia when admitted (1.14 mEq/liter). The T-wave abnormality disappeared after three days of small i.v. doses of magnesium (Luomamaki *et al.* 1975).

The study by Härtel *et al.* (1969) in Finland showed less frequency of abnormal ECG findings (Table 9-7) than did the American and English studies reported by Alexander (1968) and Brigden and Robinson (1964). They commented that the frequency of ECG abnormalities was about the same in the alcoholics as it was in other groups of Finnish men of the same age. They commented that the pattern of drinking in Finland differed from the chronic alcoholism of the patients in Alexander's (1968) and Brigden's and Robinson's (1964) studies, in that 80% of their patients were intermittent drinkers, eating amply between "binges." A point requir-

ing clarification is whether the ECG abnormalities found in nonalcoholic Finns (in rural areas) might be related to the high incidence of sudden death from ischemic heart disease in north and eastern Finland. The study by Härtel *et al.* (1969) was done in Helsinki, in the southeast of Finland. In that study, however, 42% of their patients had hypomagnesemia, but they did not correlate the ECG abnormalities with the low serum levels of magnesium, except for its occurrence in 3 of their 7 patients who had prolonged QT intervals. They confirmed the observation of T. James and Bear (1967) that the sinus tachycardia seemed to be mediated by catecholamines, since it was depressed in 17 of 21 patients by β-adrenergic blockade. Although acetaldehyde perfusion of the sinus node of dogs caused sinus tachycardia (James and Bear, 1967), and abnormal alcohol metabolism to acetaldehyde was therefore implicated, it is possible that magnesium-deficiency-induced catecholamine release might be contributory, since magnesium deficiency from many causes has also caused tachycardia and ECG changes, such as are seen in alcoholism.

Only rarely has the electrocardiographic response of alcoholic arrhythmia to magnesium been recorded. The tracing by Benchimol and Schlesinger (1953) is included in Fig. 9-8 (line C), with the proved Mg-depletion ECG of Kellaway and Ewen (1962) given for comparison in line A. Randall *et al.* (1959) mentioned that his patients with ECG abnormalities (QT prolongation, depressed ST segment and T wave), several of whom were chronic alcoholics with and without cirrhosis, showed improvement of all signs, including the abnormal ECGs when they were treated with magnesium sulfate. One of the hypomagnesemic patients of Fankushen *et al.* (1964) had sinus tachycardia and a prolonged QT interval that persisted after all of the previously abnormal serum electrolytes had returned to normal, except her hypomagnesemia. She was then given magnesium supplements, with resultant elevation of her serum magnesium to normal, whereupon she again began to drink heavily. Loeb *et al.* (1968) reported an alcoholic young woman with paroxysmal tachycardia and serum magnesium levels of 0.5–0.7 mEq/liter. She had an ECG pattern characterized by QT prolongation preceding appearance of bigeminy, multifocal ventricular complexes, and ventricular fibrillation terminating spontaneously in sinus rhythm. Despite her severe hypomagnesemia, which was associated with episodes of syncope and tonic convulsions, she was not given magnesium, but treated traditionally for her cardiac problem with procainamide, dephenylhydantoin, potassium, calcium chloride, and 50% dextrose—all of which were ineffective. The arrhythmia finally responded to artificial cardiac pacing.

Among the hypomagnesemic patients of Bajpai *et al.* (1971/1973) with characteristic ECG abnormalities that responded to rapid magnesium injections (80 mEq as the sulfate in 15 ml 25% glucose) were four with decompensated hepatic cirrhosis (etiology not designated), whose hypomagnesemic ECG changes developed after furosemide treatment. Within 15 min of the magnesium injection, at a time that the serum magnesium had risen to 1.85–2.05 mEq/liter, the ECGs showed rapid increases in PQRS voltages and lesser increases in T waves. With slow oral magnesium replenishment (as in their patients with malabsorption), the T-wave voltage improved as well (Fig. 9-9).

Until Iseri *et al.* (1975, 1978) reported electrocardiographic improvement on magnesium therapy of two alcoholic patients with arrhythmias refractory to standard treatment, the hypomagnesemia of alcohol withdrawal has been commonly disregarded, as improving on ethanol discontinuation and resumption of normal

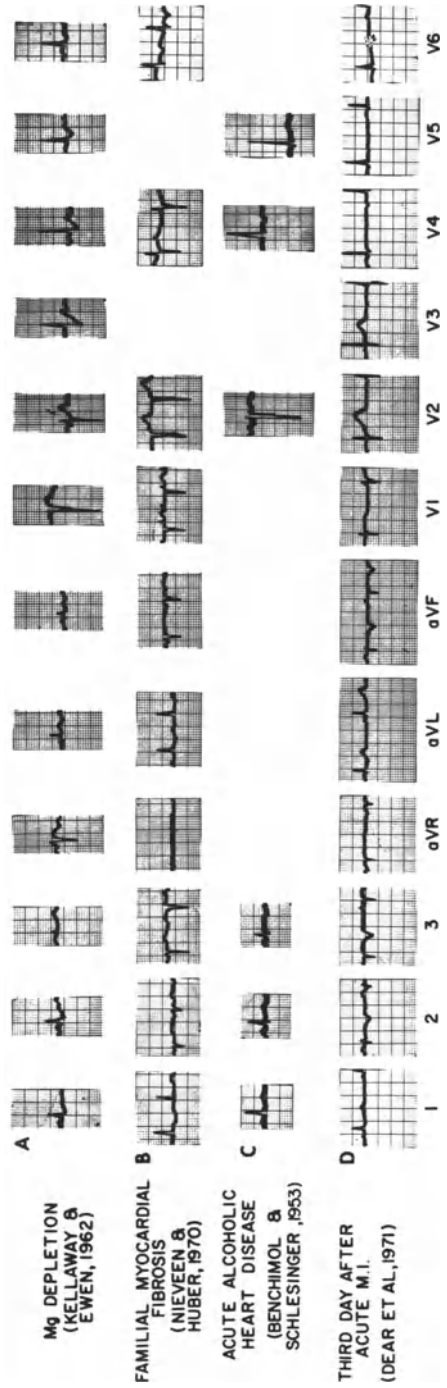

FIGURE 9-8. Comparison of electrocardiograms from a patient with acute Mg depletion and from patients with familial myocardial fibrosis, alcoholic cardiomyopathy, and postinfarction.

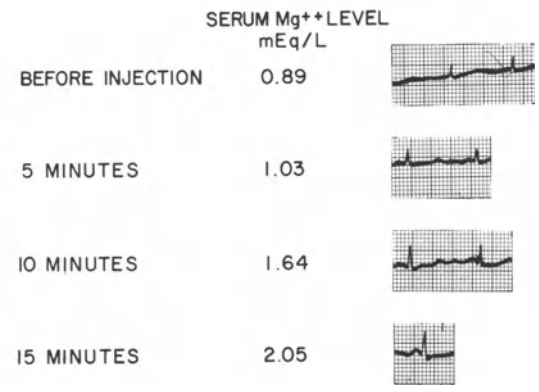

FIGURE 9-9. Electrocardiograms of cirrhotic patient after furosemide: response to i.v. magnesium. (From Bajpai *et al.*, 1971/1973.)

diet. Iseri *et al.* (1975) concerned themselves with the probable cellular magnesium deficiency of these patients and included magnesium in their treatment regimen. Their first patient had sinus tachycardia and deeply inverted T waves on admission. She then developed ventricular fibrillation, was countershocked and given lidocaine and procainamide, which was effective for about 12 hours. Recurrent episodes of ventricular fibrillation were repeatedly treated similarly. When she was given 10 ml of 20% magnesium sulfate over a 1-min period, the fibrillation was abolished. (Serum magnesium, taken before the magnesium bolus was given, was 1.39 mEq/liter.) Sinus rhythm was maintained with infusion of lidocaine (2 mg/min) and magnesium (20 mg/min), and oral quinidine at 200 ml every 4 hours. After she had received 15 g of magnesium sulfate by infusion over an 8-hr period, she again developed ventricular tachycardia. It did not respond to lidocaine but did to another 10 ml intravenous injection of 20% magnesium sulfate. She was given 5 g more of the magnesium sulfate, had the lidocaine stopped, but was continued on oral quinidine and given potassium chloride for rapidly developing hypokalemia. Their second patient had congestive heart failure, accelerated junctional rhythm, and flat T waves. After digitalis and furosemide, he developed atrial tachycardia and multiple ventricular beats and runs of ventricular tachycardia, resistant to lidocaine. He was treated with magnesium, as had been the first patient, and his ventricular arrhythmia was immediately abolished. Both patients had been treated with digitalis: the first had levels that were well below toxic; the second had digitoxicity, as well as a history of chronic alcoholism. The authors considered the refractory arrhythmia of both patients to be secondary to magnesium depletion and that the second case was complicated by digitoxicity. (They reviewed the literature on the role of magnesium loss, caused by digitalis and diuretics in cardiac patients.) They recommended magnesium therapy for the treatment of cardiac arrhythmias, whether alcohol- or digitalis-induced, or spontaneous. The general regimen recommended is 10–15 ml of 20% magnesium sulfate intravenously over 1 min, followed by a slow 4- to 6-hour infusion of 500 ml 2% magnesium sulfate in 5% dextrose in water, the infusion to be repeated if arrhythmia recurs.

Flink (1969) formulated a magnesium-treatment program for the hypomagnesemia of alcoholism, which should be applicable to the cardiomyopathy and ECG

abnormalities of alcoholism, as well as to the more commonly reported neuropsychiatric manifestations. He suggests continuous intravenous infusions for 48–60 hours, providing 50 to no more than 100 mEq of magnesium every 12 hours, or 16 mEq of magnesium (2 g of 50% $MgSO_4$ solution intramuscularly) every two to six hours for about five days. In 1969, Flink's group suggested that it is at least as appropriate to replace magnesium by the parenteral route in chronic alcoholism as it is to replace potassium or other electrolyte deficits. Flink (1976/1980) expressed surprise that, of the nutrients known to be deficient in alcoholics, magnesium alone is rarely considered in replacement therapy. As recently as September, 1977, Fisher and Avrams described the response of an alcoholic with tachyarrhythmia to low dosage $MgSO_4$ (1 ml every 6 hours) plus procainamide, but commented that although hypomagnesia of alcoholism is well-documented, its replacement remains controversial. This evoked letters to the editor from Flink (1978) and Moore (1978), who reiterated the importance of adequate magnesium repletion.

9.3.6. Dysrhythmia in Diabetes Mellitus

Disease of cardiac-conducting tissue is more frequent in diabetic patients than in other disease categories (Rubler *et al.*, 1975). Among 45 patients with idiopathic complete or partial heart block, 25% were known diabetics, and 34% more had abnormal glucose levels. McMullen (1977) reported an adolescent diabetic girl who developed sudden asystolic arrest while her diabetes was improving on conventional treatment. After reinstituting cardiac activity by classic procedures, she was found to have severe hypomagnesemia (0.6 mEq/liter). She was immediately repleted with 120 mEq of magnesium i.v. over the next 6 hours; there was gradual return of normal cardiac rhythm without further antiarrhythmic drugs.

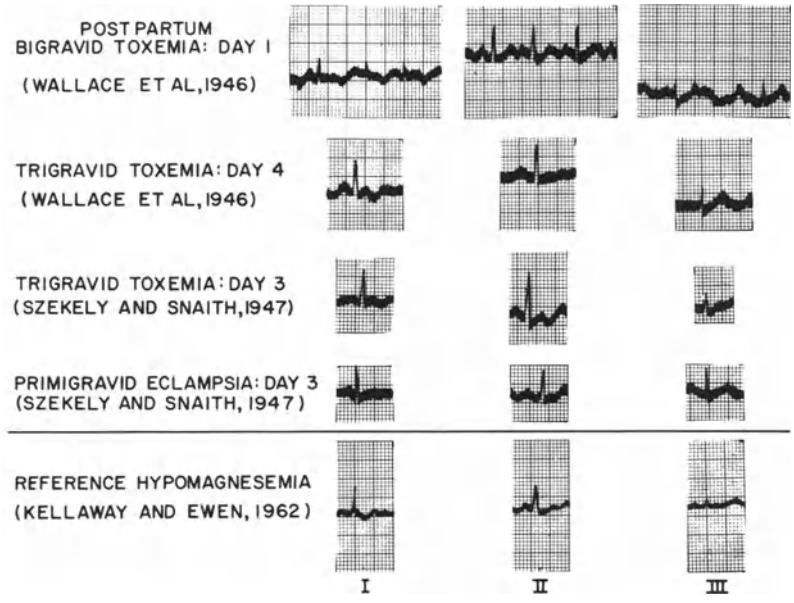

FIGURE 9-10. Electrocardiograms from patients with peripartal cariomyopathy.

9.3.7. *Arrhythmias and Abnormal ECGs in Toxemias of Pregnancy and Peripartal Cardiomyopathy*

Toxemia of pregnancy is a condition in which magnesium deficiency has been implicated and in which ECG changes not unlike those seen in severe magnesium deficiency have been recorded (Fig. 9-10). The illustration depicts ECGs from patients who developed heart failure toward the end of pregnancy or in the early postpartum period. The first report of ECG changes found were in 1937 (Gouley *et al.*; inversion of T waves was described. Hull and Hakfesbring (1937) and Hull and Hidden (1938) commented the most common abnormality seen in postpartal heart failure is low or inverted T waves, and that gallop rhythm is common. Thomson *et al.* (1938) reported that most toxemic patients had abnormal T waves, and that even 7.7% of normal pregnant women had abnormal T waves in a chest lead, that reverted to normal some time after delivery. Dexter and Weiss (1941) commented that the heart was usually normal in mild toxemia but found postpartum ECG abnormalities in 2 of 12 patients on days 6 and 9, respectively. One of them had exhibited hypertension and developed heart failure 7 days before term, but had a normal ECG; 9 days postpartum the tracing showed inverted T waves in leads I and IVF. Dieckman (1942) concurred that patients with mild toxemia rarely show cardiac damage, but found that those with severe preeclampsia and eclampsia usually had tachycardia and sometimes developed heart failure. Freundlich (1946) reported tachycardia and ventricular extrasystoles in a woman with a negative cardiac history until the birth of her second child. In their study of ECGs of 12 women with toxemias of pregnancy, Wallace *et al.* (1946) reported less severe ECG changes in 4, who did not develop heart failure, than in 2 who went into postpartum cardiac decompensation. One toxemic woman had T-wave inversion; a comparable tracing was obtained from 1 of 5 women who had normal pregnancies. They suggested that the focal myocardial necrosis that is sometimes seen in women with toxemic pregnancies is a probable cause of the T-wave abnormalities, and might be a factor in postpartum cardiac failure. Szekely and Snaith (1947) found ECG abnormalities in 7 of 19 unselected (most severe) cases of toxemia of pregnancy. They exhibited transient alterations of the T waves, usually in both standard and chest leads, similar to those seen in anterior myocardial infarction (and similar to magnesium deficiency ECG). Sinus tachycardia was frequent, and 2 had extrasystoles. Three of the patients had left ventricular failure, and the authors considered the electrocardiographic changes in at least 5 indicative of myocardial damage. Although the cardiac changes seemed to be temporary in most, their duration varied considerably, and sometimes worsened in the postpartum period. Melvin (1947) noted QRS complexes of low amplitude and low voltage or inverted T_1, T_2, and T_4 and sinus tachycardia in four patients with postpartum heart failure, with a definitely prolonged QT interval in one. Decherd and Herrmann (1944) reported supraventricular tachycardia in a woman with cardiac failure 2 months after premature termination of her second complicated pregnancy, and commented on the rapidity with which her tachycardia stopped (temporarily) when her circulation time was tested with a magnesium sulfate injection. Serial ECGs were obtained in 10 of 15 patients with myocardial failure developing in the last trimester of pregnancy and the puerperium (Meadows, 1957). In each instance, the admission ECG showed T-wave inversion in multiple limb and precordial leads. None showed significant Q

waves or conduction defects. In 5 patients, the ECGs became normal within 1–7½ months, and some improvement was seen 9–19 months later in 4. Preeclampsia had been diagnosed in only 3 of this series of 15 patients with peripartal cardiomyopathy. Seftel and Susser (1961) found normal ECGs in only 3 of 23 patients in Africa with peripartum cardiac failure.

J. B. Johnson *et al.* (1966) found low QRS voltage and absent or inverted T waves in the limb leads, and discordant T waves in leads V_1–V_6, in a 14-year-old mother of twins who had cardiomyopathy diagnosed by biopsy four months after delivery, following cardiac decompensation that developed during her third trimester. She was very sensitive to digitalis toxicity and died seven months after delivery.

Walsh *et al.* (1965) reported transitory rhythm disturbances: bigeminy, trigeminy, and multiple unifocal and multifocal premature ventricular contractions in a series of 15 patients in Jamaica, most of whom were malnourished young multipara.

Left bundle branch block, frequent extrasystoles, and P-R prolongation were seen in some or all of 7 (out of 10) patients with cardiomyopathy of pregnancy and the puerperium reported by Stuart (1968). This investigator commented that the changes are indicative of focal myocardial damage, and are in keeping with the frequent occurrence of angina in patients with peripartal cardiomyopathy with often persistent ECG abnormalities (Meadows, 1957; Gilchrist, 1963), and with the high prevalence of angina and electrocardiographic evidence of focal myocaridal lesions in patients from the same population group (Jamacia) with idiopathic cardiomegaly (Stuart and Hayes, 1963; Fodor *et al.*, 1964). Sakakikibara *et al.* (1970) reported right bundle branch block, abnormal Q waves, and flattened or inverted T waves in a woman with postpartum cardiomyopathy, confirmed by electron microscopy of a biopsy specimen.

Ledingham *et al.* (1968), after reporting a young woman who suddenly developed a cerebrovascular accident while under observation for minor antepartum bleeding, and who died despite heroic measures (including caesarean section in a hyperbaric chamber), commented on the desirability of ECG screening of pregnant patients. Their patient had an enlarged heart, triple rhythm, sinus tachycardia, and typical ECG abnormalities of cardiomyopathy of pregnancy, which was confirmed at autopsy. Despite her antemortem findings suggestive of cardiac disease, she had been considered in good health before hospital admission, and the initial ECG (only lead LI) showed only sinus tachycardia. The investigators doubted that their patient's stroke was caused by an embolus; they considered it more likely to have resulted from acute cerebral perfusion failure that might have been caused by severe hypotension associated with transient arrhythmia. They urge screening all pregnant women with 12-lead electrocardiography, to detect all unexplained abnormalities, and to arrange for immediate hospital admission if early signs of decompensation occur.

This is an excellent suggestion, that should be modified by inclusion of screening for occult magnesium deficiency by testing for percentage-retention of a parenteral load of magnesium. Whether infantile and peripartal cardiomyopathies would be reduced in incidence by treatment of pregnant women whose magnesium retention indicates deficiency should be studied. Until definitive results are obtained, this is a benign means of therapy that should be tried once ECG abnormalities are detected. Reference should be made here to the improved maternal response and fetal salvage of eclamptic women treated with magnesium salts, as compared with

those treated with diuretics, sedatives, or antihypertensives (Zuspan and Ward, 1965).

9.3.8. *Infantile Arrhythmias and Cardiomyopathies*

Congenital electrical disturbances of the heart would be expected to be manifest very early in life. Possibly arrhythmias might contribute to the sudden-infant-death syndrome (SIDS). T. James (1976, 1968) and Ferris (1972, 1973) have proposed that a contributory abnormality might be damage to the small coronary arteries that cause myocardial damage involving the conducting system of the heart. In a provocative brief report of examination of myocardial and conduction tissue of infants who had died of SIDS and of 22 control infants (who had died of traumatic, infective, or other identified cause), W. Anderson *et al.* (1970) found degenerative changes in areas including portions of the A-V node and bundle of His in all of the infants. An infant born with A-V block, who soon developed congestive heart failure and died at two months of age, had degenerative changes and calcification in the central body of the A-V bundle, fibrosis in the left bundle branch, and subendocardial calcification adjacent to the right bundle branch (R. A. Miller *et al.*, 1972). Kariv *et al.* (1964, 1971) observed that the familial form of cardiomyopathy, which begins very early in life, is characterized by arrhythmia, and that this suggests very early development of histopathologic changes. Arteriosclerosis of large and small coronaries, and focal myocardial necrosis and fibrosis, have been found in infants who died suddenly and in others who had been ill with clinically manifest heart disease, many of whose first cardiac manifestations developed at about two to four months of age, the age of peak incidence of SIDS. It seems possible that a factor that might cause fatal arrhythmia and cardiac arrest in some infants might cause silent cardiac damage permitting longer survival in some, and "benign" silent arrhythmias in others, depending on the area affected and complicating factors (e.g., infection, congestion, and their treatment).

ECG evidence of myocardial ischemia, but no reported coronary lesions, has been reported among infants with "primary" or idiopathic myocardial disease (Freundlich *et al.*, 1964). Paroxysmal atrial tachycardia and arrhythmias, including conduction blocks, multiple premature ventricular beats, and intraventricular conduction disturbances, with and without familial or isolated cardiomyopathy, has been reported in infancy (Freundlich *et al.*, 1964; Kariv *et al.*, 1964; Lev *et al.*, 1967; Simcha and Bonham-Carter, 1971; Haese *et al.*, 1972; Bove and Schwartz, 1973). The pattern of arrhythmias of the familial form of cardiomyopathy, beginning very early in life, has suggested early development of histopathologic changes (Kariv *et al.*, 1964).

That conduction defects can develop prenatally is demonstrated by bradycardia and A-V dissociation that had been found *in utero* in two infants who died with focal myocardial necrosis within three days of birth (Oppenheimer and Esterly, 1967). Paroxysmal atrial tachycardia (PAT) developed at two months of age in a previously healthy infant (Bove and Schwartz, 1973). Digoxin converted the condition to normal sinus rhythm but preexcitation persisted despite continued digitalization. She developed normally for the next half year until three days before her death. Her PAT recurred and she was given intramuscular digitalis and morphine,

to which the PAT did not respond. Intravenous phenylephrine was started and promptly stopped when multiple premature ventricular contractions developed. Ventricular fibrillation ensued, which responded to a single direct current shock, after which she developed bradycardia with ventricular bigeminy followed by brief periods of junctional tachycardia with premature ventricular contractions. She then returned to supraventricular tachycardia. On transfer to the Medical Center, she repeatedly required direct current cardioversion. She remained stable for 14 hours with a cardiac rate of 140/min after a pacing wire was placed. When ventricular fibrillation recurred, she developed profound hypotension, for which she was given intravenous infusions of isoproterenol and epinephrine. She died 48 hours after admission and was found to have cardiomegaly and lipid cardiomyopathy. The baby reported by Lev *et al.* (1967) developed a conduction defect at 12½ months, after having been alert and healthy for his first year of life. He died after a month of hospitalization, during which he exhibited intermittent 2:1 block with Adams–Stokes episodes. At autopsy, he had severe intimal proliferation encroaching on the lumen and degenerated and partially calcified elastica of the main coronary arteries and some of the branches. There were no atheromata. Numerous large and small recent, organizing, and old infarcts were present throughout the septum and free wall of the left ventricle. Atrioventricular dissociation and ventricular arrhythmias suddenly developed in a 16-month-old girl, who had been in excellent health (Haese *et al.*, 1972). During the ensuing 18 days, she had repeated episodes in association with vomiting, pallor, and cyanosis before dying with multifocal premature ventricular contractions. No light microscopic lesions of the conduction system were found, but there were numerous random foci of myocardial degenerative changes. Endocardial fibroelastosis has also caused comparable arrhythmias: heart block, atrial fibrillation, nodal tachycardia, frequent ventricular premature contractions, flattened or inverted T wave (Moller *et al.*, 1964).

ECG tracings from a 39-year-old man, who died 2 years later of familial myocardial fibrosis, disclosed auricular flutter and occasional ventricular ectopic beats with flat and negative T waves in several leads (Nieveen and Huber, 1970).

9.3.9. "Idiopathic" and Postinfarct ECG Abnormalities That May Be Related to Magnesium Deficiency or Loss

9.3.9.1. "Benign" Arrhythmias

Many cardiac electrical disturbances occur without detectable heart disease (Kastor, 1973). Their cause is unknown. Among the abnormalities reported in hearts diagnosed as "healthy" are paroxysmal atrial fibrillation (Peter *et al.*, 1968), supraventricular tachycardia (Cass, 1967), bundle-branch blocks (Beach *et al.*, 1969; R. F. Smith *et al.*, 1970), "benign" premature ventricular beats and parasystoles (Myburgh and Lewis, 1971), and even some cases of paroxysmal ventricular tachycardia (Lesch *et al.*, 1967). Kastor (1973), who presented this complex of "benign" electrical disturbances, commented that people with such abnormal ECGs cannot be distinguished from normal subjects by any specific pathological abnormality. He suggested that reentrant arrhythmias with preexcitation [the Wolff–Parkinson–White (W-P-W) syndrome] might represent a form of congenital

heart disease, as might cases of sinus node disorders (Spellburg, 1971). He points out that fibrosis of the peripheral bundle blocks might be responsible, and that since it occurs in the absence of evidence of coronary artery, myocardial, or infectious disease it, like the other cited "benign" arrhythmias, can be categorized only by the functional disorder, or the presence of fibrosis of unknown cause. The tachyarrhythmias of the W-P-W syndrome are predominantly paroxysmal supraventricular tachycardia (in 70–80% of the cases) and atrial flutter fibrillation (Tonkin *et al.*, 1976).

9.3.9.2. Similarity to ECGs of Magnesium Deficiency

The similarity of the "benign" arrhythmias of unknown cause (Kastor, 1973) and that seen in the patient with familial myocardial fibrosis with those of experimental and clinical magnesium deficiency is provocative. Comparison of the tracings obtained from Kellaway's and Ewen's (1962) patient during her acute magnesium depletion and that of Nieveen and Huber (1970) show remarkable similarities. Very-thick-walled arterioles were seen in a muscle biopsy taken from the patient with familial myocardial fibrosis (Nieveen and Huber, 1970). Possibly he also had comparable arteriolar thickening, with a small lumen/wall ratio in the myocardium, as has been reported in magnesium deficiency and in infants and children from ethnic groups with high suspectibility to early IHD. T. James (1967) has noted the similarity of the lesions of those with pathology of the small coronary arteries to those seen in magnesium deficiency and has considered the possibility that small coronary artery disease, as it causes loss of more and more small foci of the myocardium, may play a role in the pathogenesis of arrhythmias, conduction abnormalities, and sudden death in young victims. He pointed out that if the damaged myocardial foci involve conductive tissue, arrhythmias can ensue. It is well to recall, here, that the interventricular septum has a high magnesium concentration, most of which is readily exchangeable, and which can thus readily be mobilized from the heart, particularly under conditions of stress.

Intramyocardial occlusive coronary lesions and chronic inflammatory microlesions of the myocardium have been found with high frequency in adults who died suddenly and unexpectedly of ischemic heart disease (IHD), as compared with chronic IHD and controls: $p < 0.001$ (Haerem, 1975). These myocardial lesions were considered likely to render the myocardium especially vulnerable to disturbances of coronary blood flow. Haerem (1975) found that fibrous lesions in the conduction nodes were comparable in the 46 sudden death patients and the 21 patients who died with chronic coronary disease. However, nonfibrous lesions of the atrioventricular node or the bundle of His predominated among the sudden death victims ($p < 0.05$).

There is substantial attention being paid to the occurrence of fatal IHD without postmortem evidence of occlusive arterial disease (Review: Bajusz, 1965b; Baroldi, 1969, 1970/1972). Also there is increasing evidence that clinically suspect IHD need not be corroborated by demonstrable or sustained occlusion or narrowed major coronary arteries (Dear *et al.*, 1971; Neill *et al.*, 1972; Oliva *et al.*, 1973; R. Henderson *et al.*, 1973; Khan and Haywood, 1974; Brest *et al.*, 1974; Maseri *et al.*,

1975; Haywood *et al.*, 1976), in some instances in teenaged boys (Kimbris *et al.*, 1972; Sidd *et al.*, 1970). Intermittent coronary spasms have been implicated, ever since Prinzmetal *et al.* (1960) described the variant form of angina that occurs at rest. However, most patients with this disorder have severely narrowed major coronary arteries (MacAlpin, 1973; Arnett and Roberts, 1976). Similarly, necropsy studies have generally confirmed that acute myocardial infarction is associated with old coronary atherosclerotic plaques. Arnett and Roberts (1976) have considered factors that might explain normal (major) coronary arteries in patients who have had infarctions. They commented that patients with myocardial scars despite normal coronaries fall into several groups; (1) those that have left ventricular outflow obstruction (whose lesions are usually subendocardial or in the left papillary muscles), (2) whose intramyocardial arteries only were affected, or (3) who had had an embolus that subsequently lysed or recanalized. The first two categories fit well into the manifestations seen in experimental magnesium deficiency and in many cases of infantile cardiovascular disease that resemble the lesions of magnesium deficiency.

Bajusz (1965b) criticized the classical correlation of myocardial infarction or angina pectoris with anatomical (i.e., major coronary) arterial lesions as mechanistic and one-sided. He proposed that chronic coronary lesions might act as conditioning factors that predispose to myocardial necrosis by metabolic derangements that lead to electrolyte shifts in the myocardium. Such shifts, which are similar in diverse cardiomyopathies, all of which are characterized by myocardial magnesium loss as a consistent early finding (Lehr *et al.*, 1976/1980), can explain the similarity to magnesium deficiency ECGs of electrocardiographic tracings in diverse clinical conditions (including those of chronic ischemia and those seen several days after acute infarction).

It has been proposed that long-term magnesium deficiency can contribute to the atherosclerotic process. The higher incidence of sudden death from IHD in soft-water areas (low magnesium) than in hard-water areas that has been correlated with lower myocardial magnesium levels in accident victims in soft- versus hard-water areas (T. Anderson *et al.*, 1973, 1975, 1978) indicates that low magnesium levels might predispose to sudden arrhythmias. Among survivors of an acute ischemic event, further loss of myocardial magnesium (enhanced by hypoxia and stress hormones) can intensify the problem. The ECG taken at the time of the acute ischemia does not resemble that seen in acute or chronic magnesium deficiency. However, in a recording on the third day of hospitalization for an acute myocardial infarction, the first 48 hours of which had been complicated by frequent premature ventricular contractions (PVCs), episodes of sinus arrest, and A-V dissociation, the ECG resembled strongly that of the patients with magnesium depletion [Figure 9-8D (Dear *et al.*, 1971)]. The correlation of the PVCs and conduction disturbances in this patient, with the development of an ECG that resembled that of severe magnesium deficiency, might be relevant to the observation that patients with postinfarction PVCs have poorer prospects for survival than do those without premature beats. A three-year survey of over 2000 survivors of acute myocardial infarction (Coronary Drug Research Project, 1973) showed that those who had any PVCs had twice the mortality rate of those without that arrhythmia. Since such arrhythmias

are seen in magnesium deficiency, and since magnesium has been shown to be cardioprotective, use of pharmacologic doses of magnesium immediately after the acute event, followed by long-term prophylactic supplemental doses, should be tried and systematically investigated.

9.3.10. Heart Block of Dialyzed Uremic Patients

In this volume we discuss the high incidence of not only osteodystrophy but of metastatic calcification in hemodialyzed uremic patients and the suggestion that use of physiologic concentrations of magnesium in the dialysate (rather than the more commonly used low-magnesium water) might protect against such ectopic calcification. Calcific cardiomyopathy and fibrosis, involving the atrioventricular node, has resulted in heart block in such patients (R. Henderson *et al.*, 1971; Terman *et al.*, 1971; Arora *et al.*, 1975). The magnesium concentration of the dialysate was not given, and in only one report (of six patients with severe myocardial calcification) were serum predialysis (but not postdialysis levels) reported (Terman *et al.*, 1971). The predialysis serum levels in that study were only slightly elevated, but in view of the authors' published concern that high magnesium bone levels in renal disease patients might contribute to osteodystrophy (Alfrey and Miller, 1973), it is probable that low magnesium-water had been used for dialysis. Whether use of magnesium concentration of 1.5 mEq/liter in the dialysate would protect against metastatic calcification as has been proposed by Posen and Kaye (1967), Kleeman *et al.* (1970), and Danesh *et al.* (1970), and whether such cardiac damage and dysrhythmias might thereby be averted in patients receiving long-term dialysis requires study.

10
Therapeutic Use of Magnesium in Cardiovascular Disease

With such strong evidence that magnesium deficiency—or other factors that cause subnormal magnesium levels—can lead to functional and morphologic cardiovascular abnormalities, it is surprising that there has been so little clinical application of these findings. It is to be hoped that the detailed case reports published by Chadda *et al.* (1973b) and Iseri *et al.* (1975), in which they described rapid correction by magnesium of arrhythmias that had been refractory to the widely accepted therapeutic modalities, will stimulate others to consider magnesium treatment and evaluation of the magnesium status of patients with cardiac, and especially life-threatening arrhythmias. It must be cautioned that severe hypomagnesemia is not a necessary finding. For example, Chadda *et al.* (1973b, 1976/1980) found only slightly subnormal serum magnesium levels, but histories of diuretic intake and myocardial infarctions (which cause magnesium loss) in patients with a high incidence of ventricular ectopia. Iseri *et al.* (1975) reviewed the clinical states and drugs associated with magnesium deficiency and loss, and pointed out that magnesium deficiency can clearly exist without hypomagnesemia. They cited a reference (Loeb *et al.*, 1968) that demonstrated that hypomagnesemia can predispose to arrhythmia (which eventually responded to standard therapy without magnesium repletion). Noting the rapid response to magnesium of hypomagnesemic arrhythmias reported by others (Scheinman *et al.*, 1969; Rosefsky, 1972; Chadda *et al.*, 1973a) they instituted magnesium therapy in refractory arrhythmic patients after taking a blood specimen for pretreatment magnesium values, and affirmed the rapidity with which the arrhythmias were corrected.

Unfortunately, magnesium determinations are rarely part of the routine electrolyte evaluation of patients with arrhythmia. Even when detected, its correction may be delayed until failure of classic approaches; addition of magnesium results in rapid amelioration of rythmic disturbances (R. Singh *et al.*, 1975). Among those who have diagnosed hypomagnesemia, electrocardiographic evaluation is reported only occasionally. Thus, there are no firm data at present as to the frequency with which both abnormalities coexist. In a pilot study, Chadda *et al.* (1977) found that

among 12 patients with hypomagnesemia (7 secondary to alcoholism, 2 secondary to malabsorption and intestinal fistulae, 2 as a result of postsurgery hyperalimentation, and 1 in chronic renal failure), 10 had cardiac arrhythimas. Seven had ventricular tachycardia, fibrillation or more than 6 premature beats (VPBs) per minute, or atrial arrhythmia with hypotension. All of the patients with VPBs had a prolonged QT interval. Two patients had electrical alternans. The serious arrhythmias of 4 of the patients had been unresponsive to any treatment other than magnesium. All of the arrhythmic patients improved when magnesium was given.

When one considers the unreliability of serum magnesium as an index of the cellular magnesium status, the difficulty of correlating (occult) magnesium deficiency with ECG abnormalities or predisposing cardiomyopathies can be readily appreciated.

In this section, attention is given to the dramatic responses of arrhythmias to magnesium therapy and to the conditions in which such responses have been described. Consideration is also given to the nature of the magnesium therapy, and to the differences in results obtained when it is used simply as a pharmacologic agent, and when it is given as sustained therapy (in which event one may presume that an underlying deficit may be repaired). It is possible that prophylactic long-term use of magnesium supplements, possibly from the beginning of life, might be preventative of the cardiomyopathies and arterial lesions that predispose to arrhythmias *(supra vide)*, as well as of some skeletal and renal disorders *(infra vide)*.

10.1. Magnesium in the Treatment of Arrhythmias

Intravenous use of magnesium to correct arrhythmias was demonstrated by Seekles *et al.* (1930), who found that it was useful in reversing arrhythmia caused by calcium treatment of the convulsions and tetany of cows with "grass staggers" of early lactation. This group soon demonstrated this disorder in cows that were hypomagnesemic and showed that it developed in areas and at times when there was a high potassium/magnesium ratio in their forage (Sjollema and Seekles, 1932). In a few years this syndrome was shown to be associated with cardiovascular lesions that involved the subendocardium and the myocardium, including the Purkinje cells (Moore *et al.*, 1936). Thus, these studies of the correction by magnesium of calcium-induced arrhythmia might have been the result of correction of calcium-intensified magnesium deficiency. More recently, Ghana and Rabah (1977) have shown that magnesium reduces the vulnerability to electrically induced ventricular premature contractions (VPC) and of ventricular fibrillation (VF) of normal intact dogs, heart–lung preparations, and digitalized dogs (Table 10-1). Intravenous magnesium chloride solution, providing 100 mg of magnesium per kg of dog, increased the millivoltage tolerated by the intact dogs by 53% and over 100%, respectively, before they developed VPCs and VF. The heart–lung preparations tolerated 72% and 130% higher millivoltages before developing the VPCs and VF. Three of the digitalized dogs did not survive the VF phase before magnesium was to be given.

It is of interest that intravenous calcium, especially when given to patients with

TABLE 10-1. Effect of i.v. Magnesium Chloride Pretreatment on Arrhythmia Induced Electrically[a]

Group	Number of dogs	VPCT[b] control[d]	VPCT after magnesium[d,e]	*P* value	VFT[c] control[d]	VFT after magnesium[d,e]	*P* value
Intact control dogs	9	0.19 ± 0.01	0.29 ± 0.03	<0.01	0.50 ± 0.06	1.54 ± 0.70	<0.01
Intact digitalized dogs	7	0.18 ± 0.01	0.35 ± 0.04	<0.02	0.47 ± 0.09	0.89 ± 0.08[f]	<0.05
Heart–lung preparations	4	0.29 ± 0.06	0.50 ± 0.09	<0.01	0.49 ± 0.10	1.13 ± 0.27	<0.05

[a]From Ghani and Rabah (1977).
[b]Ventricular premature contraction threshold (millivolts).
[c]Ventricular fibrillation threshold (millivolts).
[d]± Standard deviation.
[e]100 mg/kg of magnesium.
[f]Based on only 4 dogs (3 died during control period).

arrhythmias of digitalis toxicity, has had serious, sometimes catastrophic, effects (Lloyd, 1928; Bower and Mengel, 1936; Berliner, 1936; Golden and Brams, 1938). The potentiation of toxicity of cardiac glycosides, not only by calcium, but by other agents (e.g., catecholamines) that increase myocardial uptake of calcium suggest that potentiation of calcium influx into the myocardium by cardiotonic alkaloids (Review: Nayler, 1967) is potentially harmful. Cardiotonics simultaneously cause magnesium efflux from the myocardium (Hochrein *et al.*, 1967; Wilke and Malorney, 1971) and inhibit magnesium-dependent cardiac mitochondrial and microsomal enzymes (Review: Seelig, 1972). Relevant to these findings is the observation that quinidine causes focal mitochondrial damage (Hiott and Howell, 1971) and that both magnesium and potassium chloride have significantly ($p < 0.001$) reduced cardiac necrosis caused by digitoxin (Savoie *et al.*, 1969).

Noting the risk of using intravenous calcium in measuring circulation time, which even in noncardiac patients causes flattened or inverted T waves in 92% of the subjects, flattened or inverted P waves in 54%, and marked bradycardia in 67%, M. Bernstein and Simkins (1939a,b) contrasted the effects of magnesium as a circulation-time reagent. They investigated the electrocardiographic effects of 10 ml of 10% magnesium sulfate solution (100 mg of magnesium) in 100 patients: 66 with and 34 without cardiovascular disease. They found no deleterious effects on the heart. There were inconsistent ECG changes in 26 of the 66 cardiac patients during or after the injection that were limited to the T waves and the QRS complexes (usually increased amplitude). Comparable benign changes were seen in 10 of 34 noncardiovascular disease patients. They had undertaken the study because of the statement that had been made that "sudden death following the injection of a magnesium salt . . . is not an uncommon occurrence," and the demonstration (with massive doses of magnesium) that magnesium adversely affected cardiac rhythmicity (J. R. Miller and VanDellen, 1938). P. K. Smith *et al.* (1939) demonstrated, for example, that cardiac arrest could indeed be produced by magnesium, but not below serum magnesium levels of 27 to 44 mEq/liter. Thus, it is important to distinguish between pharmacologic doses of magnesium, such as are used in the treatment of arrhythmias, and toxic doses. Serum levels of magnesium should be kept below 5.5 mEq/liter (Iseri *et al.*, 1975; Iseri and Bures, 1978), which gives an ample safety margin. Only levels above 10 mEq/liter have been shown to cause toxicity (Review: Engbaek, 1952).

10.1.1. Magnesium and Digitalis Arrhythmias

B. M. Cohen (1952), who reviewed digitalis toxicity and its treatment, summed up the arrhythmias produced (nodal and paroxysmal tachycardias, ventricular extrasystoles often producing bigeminy or trigeminy, and heart block) and mentioned contraindications of digitalis therapy, including paroxysmal ventricular tachycardia, and coronary insufficiency without cardiac failure. He also cited the risk of calcium therapy in digitalized patients and the additive toxic effects of digitalis and catecholamines. It is noteworthy that the arrhythmias described are also seen in magnesium deficiency and that magnesium deficiency or loss increases susceptibility to digitalis toxicity in animal and man (Vitale *et al.*, 1961, 1963; Kleiger *et al.*, 1966; Caddell, 1967; Wacker and Parisi, 1968; Ono, 1971/1973). Furthermore, patients with digitalis toxicity not infrequently have subnormal magnesium levels (Kim *et al.*, 1961; Beller *et al.*, 1974; R. Singh *et al.*, 1976).

Magnesium's antiarrhythmic effects were first demonstrated in man in digitalis toxicity (Zwillinger, 1935). This effect has also been demonstrated experimentally (Zwillinger, 1935; Szekely, 1946; J. Stanbury and Farah, 1950; Szekely and Wynne, 1951; Gendenshtein and Karskaya, 1963; Bajusz *et al.*, 1969; Seller *et al.*, 1970a,b; Neff *et al.*, 1972; Specter *et al.*, 1975) and affirmed in man (Boyd and Scherf, 1943; Szekely, 1946; Zimdahl, 1946; Freundlich, 1946; Szekely and Wynne, 1951; R. Parsons *et al.*, 1959; Michel, 1966; Kabelitz, 1968; Condorelli, 1971/1973; Lossnitzer, 1971a,b; Rotman, 1971; Iseri *et al.*, 1975; R. Singh *et al.*, 1976; Iseri and Bures, 1978). The long time lag between the first cluster of clinical reports and the more recent observations on magnesium's efficacy in digitalis arrhythmia and in other arrhythmias is probably a consequence of its early use only as a pharmacologic agent that had transient activity and occasionally caused increased irregularity of rhythm (B. M. Cohen, 1952). Since then, the substantial evidence that loss of magnesium from the myocardium can cause cardiomyopathies that predispose to arrhythmias justifies reexamination of how best to utilize magnesium in their treatment.

10.1.2. Magnesium Treatment of Ischemic Arrhythmia

10.1.2.1. Magnesium in Experimental Hypoxic Arrhythmia (Table 10-2)

Electrocardiographic changes caused by coronary ligation in dogs have responded to intravenous infusion of magnesium salts. Harris *et al.* (1953) showed that the duration of ischemic tachycardia and ectopic rhythm was shortened in 46% of the dogs infused with magnesium as the sulfate and in 70% of the dogs infused with magnesium as the chloride, at a dose of 1 mEq/liter. Clark and Cummings (1956) found that each of three successive $MgSO_4$ infusions corrected the ischemic tachycardia and multifocal ventricular arrhythmia (J. R. Cummings, personal communication). Locke–Ringer solution lacking magnesium did not influence ischemic fibrillation, but when either 0.05 mEq or 2.0 mEq of magnesium was added—either to Ringer's solution or to 0.9% saline—there was protection against fibrillation.

TABLE 10-2. Protection Against Structural and Functional Damage of Cardiac Hypoxia by Magnesium Salts (Laboratory Models)

Model and reference	Magnesium salts	Parameter
Dogs		
Harris *et al.* (1953)	$MgSO_4$ or $MgCl_2$ } 1 mEq/liter, i.v. diluted to 20 ml, i.v.	Duration of suppression of the ectopic rate to ½ control rate $MgSO_4$: successful in 5 of 11 dogs (46 %) $MgCl_2$: successful to 9 of 13 dogs (70 %)
Dogs		
Cummings (personal communication)	$MgSO_4$: 100 mg/kg in 20 ml H_2O, i.v.	Conversion of ventricular tachycardia to sinus rhythm
Dogs		
Carden and Steinhaus (1957)	Locke–Ringer solution[b]	Protection against ventricular fibrillation
	Mg (0.05 mEq)	No protection[b]
	Mg (2.00 mEq)	↑ Fibrillation[c]
	Mg (0.05 mEq) in 0.9 % NaCl	
	Mg (2.00 mEq) in 9.0 % NaCl	
	Locke–Ringer solution[b]	
	Mg (0.05 mEq) in 5 % dextrose[c]	
Rabbits		
Weber *et al.* (1958)	Mg + K aspartate i.v. (alone and in combination)	Protection against ECG changes
Rats		
Bajusz and Selye (1960b)	Mg or K chloride, oral pretreatment for 5 days preligation	Protection against cardiac necrosis (autopsy 14 days after ligation)
Guinea pigs (*in vivo*)		
LaMarche and Royer (1965)	Mg + K aspartate, i.v. (alone and in combination)	Protection against ECG changes and against tachycardia
	Mg or KCl	Not effective
LaMarche *et al.* (1961)	Mg + K aspartate	Doubles cardiac tolerance of asphyxia (cardiac respiration)
Hochrein and Lossnitzer (1969)	K aspartate	No protection
	Mg aspartate	Some protection (less than with combination)
Rats[d]	Mg + K aspartate	Decreases loss of myocardial K
Rabbits[d] Trzebski and Lewartowski (1959)	Mg + K aspartate Mg + K chloride }	Increased coronary flow (of perfusion fluid)
	Mg + K aspartate (but not chloride)	Increased resistance to anoxia: (1) 3–7 times less reduction of systolic ampliude; (2) protection against ECG changes; (3) increased worktime
Guinea pigs[d]		
LaMarche and Royer (1965) LaMarche and Tapin (1961)	Mg + K aspartate (D-aspartate, not L-aspartate)	Negligible effect on coronary flow Protection against anoxia: (1) protection against ECG changes; (2) 35 % prolongation of time to produce 75 % reduction of systolic amplitude
Guinea pigs[d]		
Rosen *et al.* (1964)	Mg + K aspartate (1.0 mg/ml of Chenoweth solution) more effective than Mg + KCl at equivalent concentration	Increased resistance to anoxia (increased time for amplitude of heartbeat to decrease to 50 % control)
	Mg + KCl	Coronary flow increased over perfused nonanoxic heart
	Mg + K aspartate	Coronary flow increased in both nonanoxic and anoxic hearts

[a]Coronary ligation.
[b]Ringer's solution without Mg.
[c]Two milliequivalents Mg in 5 % dextrose.
[d]*In vitro* hypoxia; anoxia (isolated heart).

Dogs with persistent ventricular tachycardia and ectopic extrasystoles (after two-stage coronary ligation) responded to repeated injections (up to seven) of $MgNa_2EDTA$ solution (50–100 mg/kg body weight) by a 25% decrease in heart rate, and sometimes by transitory restoration of the sinus rhythm on the day after the ligation. The effect of the infusions were sustained somewhat longer, but were still transient, two days after the ligation (Gendenshtein and Karskaya, 1963). The aspartate salts of magnesium and potassium, in combination, were protective against ischemic ECG changes in rabbits with coronary arterial ligation (Weber *et al.*, 1958) and against ECG of asphyxia in guinea pigs (Hochrein and Lossnitzer, 1969).

Isolated hearts, under hypoxic conditions, have shown less reduction of systolic amplitude and other ECG changes of anoxia when suspended in fluids containing magnesium and potassium aspartates; chloride salts of the cations were less effective (Laborit *et al.*, 1957; Weber *et al.*, 1958; Trzebski and Lewartowski, 1959; LaMarche and Tapin, 1961; LaMarche *et al.*, 1962; H. Rosen *et al.*, 1964; LaMarche and Royer, 1965). Some of the benefit might reflect the coronary vasodilation shown to be produced by magnesium and potassium sulfate or chloride (Elek and Katz, 1942; Scott *et al.*, 1961; Review: Haddy and Seelig, 1976/1979). The aspartate salts were more effective than the chlorides in the *in vitro* studies.

10.1.2.2. Magnesium in Clinical Arrhythmias of Ischemic and Unknown Origin

Having demonstrated *in vitro* that magnesium sulfate has coronary vasodilator activity, Elek and Katz (1942) recommended its use as a pharmacologic agent in paroxysmal tachycardia associated with myocardial ischemia. Boyd and Scherf (1943) corrected paroxysmal auricular tachycardia (PAT) by giving 10–15 ml of 15% $MgSO_4$, or 10 ml of a 30% solution intravenously (in 10 of 19 treatments). Comparable dosage was effective in 9 of 13 patients with PAT and in 1 with Wolff–Parkinson–White syndrome (Szekely, 1946), restoring sinus rhythm and decreasing the

TABLE 10-3. Use of Magnesium in Clinical Arrhythmias and Ischemic Heart Disease

Condition	Magnesium treatment	Response	Investigator
Strophanthin toxicity	7–10 ml 15% $MgSO_4$ intracardiac i.v.	Prompt sinus rhythm Decreased rate	Zwillinger (1935)
Supraventricular tachycardia	5 ml 20–30% $MgSO_4$ i.v.	Attacks ceased (24 hr)	
Paroxysmal auricular tachycardia (PAT)	10–15 ml 15% $MgSO_4$ i.v.or 10 ml 30% $MgSO_4$ i.v.	Prompt sinus rhythm Decreased rate	Boyd and Scherf (1943)
Digitalis arrhythmia PAT, W-P-W syndrome	10–20 ml 20% $MgSO_4$ i.v.	Prompt response Prompt decreased rate	Szekely (1946) Szekely and Wynne (1951)
Ischemic heart disease (angina pectoris)	0.5 ml 50% $MgSO_4$ i.m. every 5 days (followed by heparin: 5000 U, 3×/wk) or 0.5–2 ml, intermittent courses	Decreased pain Decreased nitroglycerine requirement (in 24 hr)	Malkiel-Shapiro *et al.* (1956)
Acute MI	0.5 ml 50% $MgSO_4$ i.m. (followed by 0.5 ml in 12–24 hr) Then 1 ml every 3 days × 4 Then 1 ml every 5 days to discharge	Decreased mortality (1 of 64 died)	Malkiel-Shapiro (1958)

TABLE 10-3. *(Continued)*

Condition	Magnesium treatment	Response	Investigator
Chronic IHD Acute MI	2 ml 50% $MgSO_4$ + heparin 1×/wk 2 ml 50% $MgSO_4$ + more frequent heparin	Angina subsided ECG improved (↑ ST voltage) Improved lipoproteins	Parsons *et al.* (1960)
Acute MI Chronic IHD	0.2–0.5 g Mg + K aspartate i.v. 0.2–0.5 g Mg + K aspartate day p.o.	ECG improved: ↑ T voltage ↑ ST voltage ↓ Extrasystoles Repolarization rhythm	Melon (1961)
Acute MI (controlled study) Anticoagulants with and without K + Mg Followed for 0.5–2 yr	20 patients: 2 g K + Mg aspartate in i.v. infusions; then 2 g/day p.o. 25 controls	Less pain than controls 45%: complete recovery 8%: complete recovery	Tapin (1962) cited by Nieper and Blumberger (1966)
Acute MI	1.0–2.5 liters 10% glucose i.v. every 24 hr containing insulin (1 U/10 g glucose), heparin (300–400 mg), K_2HPO_4 (4 g), K + Mg aspartate (4–6 g), cocarboxylase (B_1 derivative), and cytochrome c	Rapid correction of ischemic ECG (in 4–24 hr) Rapid decrease in pain	Larcan (1963, 1966)
Acute MI	10–30% glucose (500 ml i.v.) 1 U insulin/10 g glucose Mg + K aspartate	Rapid decrease in pain	Laborit (1966)
Acute MI	5–10 % glucose (250 ml, 2 × / day) containing 40 ml 10% K + Mg aspartate for 3–4 days Then 700 mg Mg + K aspartate 4–5×/day p.o. for 2 weeks Then 700 mg Mg + K asparate 3 × /day	Decreased mortality (5 of 97 vs. 12% in earlier study without Mg + K) Dysrhythmias and ECG corrected in 2 days Rapid disappearance of shock syndrome Decreased need of analgesics	Kenter and Falkenhahn (1966)
Acute MI	5 g K + Mg aspartate by continuous i.v. infusion/24 hr for 1 wk	Prompt decrease of pain ECG: arrhythmia improved	Pillen (1966)
During recovery and chronic IHD	1 g K + Mg aspartate i.v. 3×/day Then 2–3 day in divided doses p.o. for prolonged period	Tachycardia disappeared	
Acute MI and 1 month earlier Chronic IHD	5 g K + Mg aspartate in 250 ml 5% glucose (slow i.v.): 4–5 days Then 2–4 g K + Mg aspartate p.o.	↑ QRS or disappearance of extrasystoles in 40%	Nieper and Blumberger (1966)
Acute MI during recovery (controlled study)	6 mEq K + 6 mEq Mg as aspartates in 250 ml 5% levulose 1–2×/day for 3 wk (i.v.) Thereafter p.o.	Prompt transient ECG improvement Permanent improvement after 10th infusion	Stepantschitz and Frohlich (1967)
Refractory supraventricular tachycardia and premature ventricular systoles (malabsorption syndrome)	2 ml 25% $MgSO_4$ i.v. followed by sustained oral and i.m. supplements	Prompt return to sinus rhythm ↓ No recurrence of arrhythmia	Chadda *et al.*, (1973b)
Refractory ventricular fibrillation with and without digitalis toxicity (multifocal, ventricular tachycardia)	10–15 ml 20% $MgSO_4$ i.v. in 1 min followed by slow 4–6 hr infusion of 2% $MgSO_4$ in 500 ml dextrose in water; repeat if arrhythymia recurs (avoid serum Mg > 5.5 mEq/liter)	Prompt return to sinus rhythm	Iseri *et al.* (1975)

heart rate. The latter investigator noted that the patients most responsive to magnesium therapy were those who had advanced heart disease with congestive failure. One may speculate that such patients are likely to have received long-term diuretic and cardiotonic therapy, and thus to be most magnesium depleted. Neither group found any effect of magnesium on auricular flutter or fibrillation.

Despite these early promising results, and the experience of clinicians from the British Commonwealth (England, South Africa, Australia, and England: Malkiel-Shapiro *et al.*, 1956; 1960; Malkiel-Shapiro, 1958; R. S. Parsons, 1958; Parsons *et al.*, 1959, 1960, 1961; Agranat, 1958; Marais, 1958; Teeger, 1958; Anstall *et al.*, 1959; Browne, 1961, 1963, 1964a,b; Hughes and Tonks, 1965; Tonks, 1966) with the efficacy of long-term treatment of patients with acute or chronic IHD (rationale based on magnesium's effects on blood coagulation and lipids), the clinical use of magnesium in cardiovascular disease has been slow to gain acceptance in America. It has been utilized, usually with potassium, with and without heparin, and as organic salts (e.g., nicotinate and aspartate) parenterally (with and without glucose and insulin) immediately after infarction, and orally in the management of postinfarction patients and those with angina pectoris. Such use has been described in studies from the European continent (Hoffman and Siegel, 1952; Laborit *et al.*, 1958; Melon, 1960; Thurnherr and Koch, 1962; Larcan, 1963; Perlya, 1965; Kanther, 1966; Kenter and Falkenhahn, 1966; Rigo *et al.*, 1965; Köhler, 1966; Laborit, 1966; Larcan, 1966; Maté *et al.*, 1966; Michel, 1966; Nieper and Blumberger, 1966; Pillen, 1966; Stepantschitz and Fröhlich, 1967; Savenkov *et al.*, 1971). Most of the reports have been uncontrolled clinical trials, sometimes large series of cases that were compared with prior series treated identically except for the magnesium (and potassium) salts. (Representative treatment regimens are entered on Table 10-3.)

Whether the combination of magnesium and potassium aspartate salts, given in high doses for treatment of the acute infarction and then followed by prolonged oral therapy for indefinite periods, provides better results than does the inorganic sulfate, which was somewhat similarly used only in the South African and Australian studies, cannot be averred. The studies evaluated different parameters; comparably better results were obtained with prolonged than with short-term therapy. Nieper and Blumberger (1966) refer to a controlled study with the mixture of magnesium and potassium aspartates in 45 patients with acute myocardial infarction (Tapin, 1962). Classical anticoagulant and supportive therapy was provided the 25 control patients; 2 g of magnesium and potassium aspartate were added to the daily infusions of the 20 patients in the test group until infusions were discontinued, at which time the patients were given the same daily dosage orally. [Nieper and Blumberger (1966) commented that their own experience indicates that 5 g daily in 250 mg of 5% glucose, given by slow intravenous infusion, for 4 to 5 days is preferable, to be followed by 2 to 4 g daily orally thereafter.) Nonetheless, Tapin (1962) found that, even with the low dosage used, his magnesium and potassium aspartate treatment group had a somewhat lower death rate in the hospital (40% versus 56% among those on standard therapy). The real difference was manifest among the survivors (6 months to 2 years follow-up). The magnesium and potassium aspartate-treated group showed complete recovery in 45%; only 8% of the controls recovered completely. Pillen (1966) and Nieper and Blumberger (1966), using the higher dosage regimen routinely in their acute-infarct patients, found good to excellent results

in 16 of 19 patients, and recommend immediate intravenous administration of magnesium and potassium aspartate as part of the emergency treatment, even before the patient reaches the hospital. They found rapid improvement of the ischemic ECG (within 12–24 hours), as well as rapid decrease of pain, most patients requiring no analgesic therapy.

Stepantschitz and Fröhlich (1967) compared the outcomes in three groups of patients hospitalized for six weeks after an acute myocardial infarction: Group I (114 patients) received standard supportive therapy that included oxygen, sedation, alkaloids, treatment of shock with corticosteroid and epinephrine, and antiarrhythmia agents as necessary. Group II (123 patients) were also given anticoagulants. Group III (100 patients) were given magnesium and potassium aspartate in addition to the therapeutic regimen given group II. Each patient in group III was given 6 mEq of magnesium and potassium and 12 mEq of aspartate in 250 ml of 5% levulose once or twice daily for three weeks, and the same dosage for the remaining three-week period of hospitalization. The death rate in group I was 46.5%, versus 13 and 15% in groups II and III. However, in noting the comparable mortalities in the groups receiving anticoagulants (II) and magnesium and potassium aspartate (III), the authors noted that the patients in group III had had 13 times as many recurrent infarctions as had the other two groups, and thus had the poorest prognosis. They tabulated the criteria for the effects of treatment (Table 10-4) and pointed out that the most striking advantage of the magnesium and potassium aspartate therapy was in the time taken to achieve complete freedom from pain (average of 5.3 days, versus 16.8 and 14 days in groups I and II0. The average time taken for the ECG to return to near normal was 15.5 days in group III, versus 22.3 and 23.7 days in groups I and II. Complete involution of the ECG signs of infarction occurred in 34% of the patients in group III, and in 11.4% and 17.9% of those in groups I and II.

Using the transcardiac iontophoretic method of giving magnesium to patients

TABLE 10-4. Influence of Addition of Magnesium[a] and Potassium[a] Asparate in 5% Levulose to Standard Treatment + Anticoagulants in Myocardial Infarction[b]

Changes	Group I[c] (N = 114)	Group II[d] (N = 123)	Group III[a] (N = 100)
In ECG			
Days taken to normalization (average)	22.3%	23.7%	15.5%
Complete involution of acute ischemic ECG	11.40%	17.88%	34%
ECG signs of MI on discharge	88.6%	82.1%	66%
In pain			
Days to complete freedom from pain (average)	16.9%	14 %	5.3%
Angina pectoris on discharge from hospital			
More severe, frequent attacks	37.7%	12.2%	6%
Slight, intermittent attacks	37.7%	21.9%	18%
No attacks	24.6%	65.9%	76%

[a] 6 mEq Mg; 6 mEq K, i.v. in 250 ml 5% levulose, 1–2 × / day + group II treatment.
[b] From Stepantschitz and Frölich (1967).
[c] Standard treatment (group I): Bed rest at least 6 weeks; barbiturates + alkaloids, early days; oxygen; treatment of decompensation, shock as required.
[d] Group I treatment, plus anticoagulants (group II).

with myocardial infarction, Köhler (1960) found complete to almost complete relief of pain in 88 of 100 patients, and marked improvement in 12, as compared with complete relief in none, and marked to almost complete relief in only 27 who received placebo iontophoresis. In the remaining placebo group, 34 were unchanged or worse and 36 showed only slight improvement. He later commented (Köhler, 1966) that the iontophoretic procedure carries in only the cation. Kucher (1966), using the same procedure, but with both magnesium and potassium salts, reported that 180 to 184 patients (classified as angina pectoris with myocardial degeneration) improved, and all 22 patients who had recent infarctions improved. Among those who had refractory auricular fibrillation, extrasystoles, or paroxysmal tachycardia, 9 of 16 improved.

10.1.2.3. Glucose Solutions and Insulin to Increase Myocardial Magnesium and Potassium Uptake

Laborit (1958) considered hypertonic glucose solutions useful in attaining a normal myocardial electrolyte gradient, (for repolarization) and recommended the use of aspartate salts of Mg + K. Sodi-Pallares *et al.* (1962, 1966, 1979) suggest the addition of insulin to reverse the ECG signs of ischemia. Kones (1975) has evaluated the clinical response of patients with infarction and reported that glucose–insulin–potassium therapy is a useful therapeutic adjunct. Opie and Owen (1976) have provided experimental evidence that such treatment increases the arteriovenous coronary difference of glucose, decreases the free fatty acids, accelerates the fall of the epicardial ST segment, and prevents the small rise in the ST segment in the peri-infarct and nonischemic zones. Gavrilescu *et al.* (1974) have shown that slow (over 1-hour period) i.v. infusion of 3 g of potassium and magnesium asparate in 200 ml of physiological saline lowers the elevated levels of free fatty acids that develop during the first hour after an acute myocardial infarction (p. 225).These findings support the contention that such treatment has beneficial effects on tissue metabolic, histologic, and electrocardiographic criteria of ischemic damage. In commenting on Sodi-Pallares' and Opie's findings in the clinical and experimental situation, and Sodi-Pallares' (1976) reminder that diuretics and antiarrhythmic therapy are contraindicated with the polarizing treatment, Bing (1976a,b) observed that the metabolic findings with this form of therapy might well provide a piece of the Rosetta stone. He indicated, however, that until the etiology of ischemic heart disease can better be defined, it will continue to be difficult to bridge the gap between fundamental and applied knowledge.

The data presented in this volume provide considerable evidence that cellular magnesium deficiency can be another key to the etiology of ischemic heart disease and other cardiomyopathies. Since administration of insulin and glucose has been shown to accelerate the uptake of ^{28}Mg by the heart more than twofold (Aikawa, 1960a), and the magnesium ion seems to be essential for maintaining tissue response to insulin (G. Bhattacharya, 1961), addition of magnesium to the polarizing solution would seem advisable. It is provocative that Bajusz (1964, 1965b) found that the partially protective effects of either magnesium and potassium chlorides or aspartates were markedly increased by simultaneous administration of glucose and insulin. Another justification for including magnesium in the polarizing solution is its

requirement for the enzyme systems necessary for accumulation of potassium against a concentration gradient (Review: Seelig, 1972).

A metabolic approach to the treatment of endomyofibrosis of the adult (with abnormalities of the ST segment and Q wave) incorporated magnesium and vitamin B_1 as well as insulin, glucose, and potassium, to enhance glycolytic metabolism (Michon *et al.*, 1959). Larcan (1966) later reiterated the value of this approach, using cocarboxylase (a B_1 metabolite) instead of thiamine in the treatment of patients with myocardial infarction. He stressed the importance of including magnesium. He reproduced representative ECGs from representative cases from his series of 40 cases, and commented that most striking was the much more rapid analgesic effect in the metabolically treated patients than in a control group that was treated by bed rest, anticoagulants, and opiates. Asthenia was also notably diminished, and the ischemic ECG changes regressed rapidly, the improvement beginning as early as four hours after the first ECG on hospitalization, and being definitive by the end of the first to second day of the infusions.

10.1.2.4. The Role of the Anion

In most of the clinical trials, magnesium sulfate has been the salt used, and in the United States it is the only readily available parenteral preparation. Ischemic arrhythmia in dogs responded somewhat better to magnesium chloride than to magnesium sulfate at a 1 mEq/liter dose of magnesium (A. Harris *et al.*, 1953). However, the numbers were too small for significance to be determined. Selye (1958d,) showed that not only phosphate, but also sulfate, sensitizes the heart to cardiopathic agents, whereas the chloride (of magnesium or potassium) is protective. He found no superiority of the aspartate or orotate salts of magnesium and potassium to the chloride salts as cardioprotective agents in his experimental models (Selye, 1958g). More recently a hydrochloride salt of magnesium and potassium aspartate has been investigated, and found to be better absorbed and utilized, and to be more effective than the aspartate salts in experimental cardiomyopathic models (Classen *et al.*, 1973, 1975, 1976, 1978; Ebel *et al.*, 1975). Neither magnesium sulfate nor magnesium aspartate were effective against cardiac necrosis induced by epinephrine plus a mineralocorticoid, whereas magnesium chloride and magnesium aspartate hydrochloride each exerted significant protective effects (Classen *et al.*, 1975, 1978). These investigators concluded that it is necessary to correct, not only the magnesium deficit, but the hypochloremic alkalosis in metabolic myocardial necrosis. Lehr *et al.* (1972) concur that it is necessary to provide both magnesium and chloride to protect against experimental myocardial necrosis of widely different natures (Lehr, 1965, 1969; Lehr *et al.*, 1966).

10.2. Formulation of a Metabolic Therapeutic Program for Treating Cardiomyopathies and Arrhythmias

It is important to consider all of the positive and negative findings from animal and human studies in determining a safe, effective approach to the treatment of cardiomyopathic disease, whether of ischemic or other origin. Because magnesium

deficiency or loss from the myocardium has been repeatedly implicated in experimental cardiomyopathy, and because magnesium is cardioprotective, it should be included in treatment programs, such as in the polarizing treatment. Sodi-Pallares (1969) cautions against the use of diuretics and corticoids (which cause loss of magnesium, as well as of potassium) and such inotropic drugs as digitalis, quinidine, and catecholamines, unless there is pulmonary edema or atrial fibrillation and ventricular tachycardia. Since inotropic drugs and some diuretics (e.g., thiazides) increase calcium retention and, in the case of the glycosides and catecholamines, increase myocardial calcium uptake and lipolysis, caution should also be exercised in treating hypocalcemia of cardiac patients with intravenous calcium salts. Potassium chloride is readily available and should certainly be included in the therapeutic regimen. (The author suggests that it be used with magnesium in a polarizing solution incorporating dextrose, water, and insulin.) Unfortunately, in the United States, magnesium is available for parenteral use more readily as the sulfate than as the chloride. Perhaps the aspartate–HCl salt of magnesium will become available in the United States, as it is in Europe.

Table 10-3 indicates the therapeutic regimens that have been effective in the treatment of the acute ischemic event and in hypomagnesemic arrhythmia. In open-heart surgery, magnesium has been a useful additive to the pump-prime (optimum concentration to be proved, *supra vide*) and has been used as an intravenous bolus (0.1 g/kg) to facilitate postoperative defibrillation (Buky, 1970). Magnesium chloride (100 mg Mg) has also been recommended, pre- and postoperatively, to prevent arrhythmias (Khan *et al.*, 1973; Holden, 1978). The emergency therapeutic dosage of magnesium, as described by Iseri *et al.* (1975) is recommended, with the modification that after the bolus of magnesium, the maintained infusion should be 5–10% dextrose in water plus insulin (0.1 unit/g dextrose), and potassium (3–6 mEq) and magnesium (3–6 mEq) as the chloride or aspartate hydrochloride, if available. Possibly, the water-soluble B vitamins and vitamin C should be added to the infusion in "stress-formula" concentrations. Investigations are required to determine the optimal formulation.

III

SKELETAL AND RENAL EFFECTS OF MAGNESIUM DEFICIENCY

11
Magnesium, Bone Wasting, and Mineralization

11.1. Mobilization of Bone Magnesium

Relatively little attention has been paid to the importance of magnesium in bone metabolism, except to the degree that it affects the activity of the parathyroid glands and C cells and their secretion of parathyroid hormone (PTH) and calcitonin (CT), and the response of target organs. However, experimental magnesium deficiency causes abnormalities in skeletal structure, enzymes, and mineralization that resemble some of those seen in several clinical bone diseases. Depending on the degree and duration of the magnesium deficiency and concomitant dietary or iatrogenic imbalances (of magnesium with calcium, phosphates, vitamin D, and other calcemic agents), the pathologic skeletal findings can range from osteopenias to osteosclerosis. The effects of vitamin D, calcium, and phosphorus on magnesium requirements and on skeletal responses have been intensively studied, particularly in the 1930s, when vitamin D toxicity was the focus of much attention. Many of the results are conflicting, probably due to the dietary variations, and to species differences in requirements (i.e., of vitamin D). Only those portions of the PTH/CT/Mg data that deal directly with magnesium and bone are considered here. Much of that relating to gestational abnormalities has already been discussed. The relatively little information found on heteroionic magnesium/calcium exchange in bone, and on the magnesium interrelationships between the phosphatases that affect mineralization, alkaline phosphatase and pyrophosphatase, are brought into focus as possibly providing some insight into the conflicting and confusing data on mechanisms of pathologic skeletal processes.

Largely disregarded in the treatment of bone disease is the possibility that some of the therapeutic agents (used to increase bone mineralization) might adversely affect bone metabolism by causing loss of skeletal magnesium. Calcium, phosphorus, and vitamin D all increase magnesium requirements; the intakes of all have been rising during this century, while that of magnesium has been falling. Since plasma levels of magnesium are maintained within very narrow limits, even in the face of insufficient intakes or excessive losses, the magnesium is mobilized

from the tissue stores. Bone constitutes the largest total source; it contains two-thirds of the total body magnesium (Review: Heaton, 1971). Much of bone magnesium is quite labile, especially in young animals. Were the bone magnesium merely an inert storage depot, this would be a benign means of providing magnesium for the function and structure of life-preserving tissues (e.g., cardiovascular and renal), as well as preventing acute neuromuscular signs of magnesium depletion. For short periods of time, and more in young than in older individuals, availability of bone magnesium probably serves as a safety device that prevents serious systemic signs of magnesium deficiency. However, long-term loss of magnesium from the bone causes disturbances of bone modeling, remodeling, and turnover, with resultant bone abnormalities. Depending upon the supply of the calcemic agents or phosphate, it can give rise to formation of brittle chalky bones or to osteopenia. The mobilized bone constituents contribute to the renal damage of magnesium deficiency.

Because the amount of magnesium bone is only 1/40 to 1/50 that of calcium (Duckworth *et al.*, 1940), relatively few investigators have given it much consideration as a significant bone mineral, either in bone metabolism or as a source of emergency magnesium supply. Bone magnesium is an important source, especially in young animals (McAleese *et al.*, 1961), an observation supported by the drop in bone magnesium immediately after convulsions of magnesium deficiency (Orent *et al.*, 1934; Martindale and Heaton, 1964). Differences in responses to vitamin D, PTH, and CT influence the mobilization of magnesium during magnesium deficiency and have led to diverse findings. Many of the studies have dealt with the influence of magnesium deficiency and repletion, with high and low calcium, phosphorus, and vitamin D intakes, on metabolic balance. They are not considered here, unless bone values are also given, since positive balances (e.g., of calcium and phosphorus) can be achieved by metastatic calcification, as well as by increased bone mineralization and can occur even with bone demineralization. Also, failure to exhibit negative magnesium balance under conditions that cause abnormal bone structure might be related to the initial shift of bone magnesium and calcium (e.g., the increase in bone magnesium/calcium ratio in rickets).

Some of the disparate findings in the different studies might well be the result of use of widely differing diets in the magnesium deficiency studies: diets that provide 3200 to 8000 parts per million (ppm) of calcium, 1900 to 5100 ppm of phosphorus, and 1150 to 1,000,000 IU of vitamin D per kilogram of diet mix, and 3 to 100 ppm of magnesium (Larvor and Durlach, 1971a). In some of the studies analyzed and tabulated by Larvor and Durlach (1971a), only the magnesium provided was indicated. Thus, the studies cited in the following sections are not strictly comparable.

11.2. Influence of High Vitamin D and High or Low Calcium Intakes

11.2.1. High Calcium: Decreased Mobilization

Most studies of hypervitaminosis D are in rats, which are commonly fed rations rich in calcium and phosphate, as well as in vitamin D. All three of these supple-

ments cause magnesium loss (Reviews: Heaton, 1971; Larvor and Durlach, 1971b; Seelig, 1971). High calcium intakes compete with magnesium for intestinal absorption and renal tubular reabsorption (cited reviews), and high calcium extracellular levels result in exchange of bone magnesium for calcium.

Orent *et al.* (1934) were the first to note that rats on a low-magnesium, very high-calcium diet (Mg/Ca= 5/ >3000), also fed vitamin D_2, lost about half the original percentage ash magnesium, but doubled the percentage ash calcium in their long bones. The magnesium was ⅓ normal for the same-age control rats. They noted that in rats sacrificed during convulsions, the magnesium level rose in the blood and dropped sharply in the bones, suggesting rapid mobilization of bone magnesium at that time. Nonetheless, the total accretion of bone magnesium exceeded the amount fed, and the authors speculated that it might have derived from organs such as liver, kidney, and heart, and possibly from muscle, organs which also increased in calcium content. They suggested that lowering of the skeletal magnesium/calcium ratio might have been caused by their having added vitamin D to the rats' rations. Comparable reduction in bone magnesium was reported by Cunningham (1936b) in rats fed the same magnesium-deficient diet (Kruse *et al.*, 1932). Watchorn and McCance (1937) provided cod liver oil rather than viosterol to the rats that they maintained on a subacute magnesium-deficient regimen for up to three months. Notable were renal calcification and hepatic and skeletal damage. The long bones and teeth were brittle, and the teeth were loose in their sockets. Even though few of the many studies of vitamin D toxicity (which emphasized renal and cardiovascular damage) provided magnesium values, some of the findings (which subsequent work suggests might have been contributed to by magnesium depletion caused by the regimens) are included here. For example, rats developed overcalcification of bones and teeth (which is suggestive of a process that inhibits mobilization of bone minerals) when they were given high-dosage vitamin D, as well as diets rich in calcium and phosphorus (L. J. Harris, 1932; Shelling and Asher, 1932). In the late stage of moderate hypervitaminosis D, or with very high doses, there were cessation of osteogenesis and bands of less calcified bone near the epiphyses. (The histological changes described are much like those reported in magnesium-deficient rats and in human osteopetrosis.) Storey (1960) noted that intermittent hypervitaminosis D produces similar lesions. Comparable hypercalcification of bones, which lost 74% of control magnesium content, was found in magnesium-deficient chicks supplemented with calcium and vitamin D (C. Reddy *et al.*, 1973). They also had increased unmineralized osteoid and cortical thickening, that was reversed rapidly on magnesium repletion. A recent study with hypervitaminosis D in pigs clarified the nature of the bone pathology with increasing doses. At 5 and 25 times the recommended dose there was osteopetrosis; at higher doses there were hypercalcemia and hypophosphatasia (Chineme *et al.*, 1976).

On the other hand, it was suggested that rats that developed hypomagnesemia during their overdosage with vitamin D, and that did not exhibit hypermagnesuria, might be depositing magnesium in their bones (Richardson and Welt, 1965). Wallach *et al.* (1966) confirmed this premise in dogs on 1% dietary calcium intake, given very high vitamin D doses, that became hypercalcemic and hypomagnesemic. Their bones had only slightly increased total calcium and moderately increased ($p < 0.2$) exchangeable calcium. Their total bone magnesium, however, had increased signif-

icantly ($p < 0.001$), but there was little change in the exchangeable magnesium content.

The total bone mineral distribution of the dogs given short-term toxic doses of vitamin D (Wallach *et al.*, 1966) resembles that reported in the early rickets studies in rats [Malcolm, 1904; Mellanby, 1926 (cited by McHargue and Roy, 1930)]. Since these animals were hypomagnesemic, as were rats overdosed with vitamin D (Hanna, 1961a; Harrison and Harrison, 1964), it can be speculated that they were in the early stage of development of vitamin-D-resistant rickets (i.e., hypervitaminosis D rickets: Ham and Lewis, 1934). Longer-term hypervitaminosis D plus high calcium intakes, as in the Watchorn and McCance (1937) and Storey (1960) studies, might be experimental models of infantile hypercalcemia, which is associated with osteosclerosis, as well as with metastatic calcification (Review: Seelig, 1969b).

Despite the magnesium loss caused by the vitamin D and calcium excesses, caution must be exercised in repleting the magnesium. Whittier and Freeman (1971) have demonstrated that metastatic calcification has been potentiated by giving magnesium to rats with hypercalcemia caused by hypervitaminosis D. This recalls the speculation that the use of magnesium laxatives, to manage the obstipation of hypercalcemic children, might have contributed to their metastatic calcification (Creery, 1953; Lowe *et al.*, 1954; Review: Forfar thesis). The rationale for this paradoxical observation is considered elsewhere in this chapter. It is important to keep in mind now that hypophosphatemic rickets, refractory to high dosage vitamin D and calcium, has been reported to be responsive to magnesium.

Fetal and neonatal spontaneous fractures and lesions resembling those of osteogenesis imperfecta and hypophosphatasia develop in pups of rats given high doses of vitamin D and in infants born with intrauterine growth retardation, both conditions that might be related to fetal magnesium deficiency.

Early or acute magnesium deficiency has been shown to stimulate PTH secretion, but the concomitant hypercalcemia in the experimental model and most clinical conditions in which hypervitaminosis D plus high calcium intakes play a role would function to decrease PTH secretion, outweighing the stimulant effect of magnesium deficiency. Additionally, early and acute magnesium deficiency has stimulated CT secretion, an effect enhanced by hypercalcemia (Stachura and Pearse, 1970). Thus, the overall effect on bone of diets low in magnesium and high in calcemic agents is decreased mobilization of bone calcium, with replacement of surface bone magnesium by calcium.

11.2.2. Low Calcium: Increased Mobilization

Rats on normal diets given high-dosage vitamin D without calcium supplements or low-calcium diets were shown, in early studies, to exhibit resorption of compact bone, an effect attributed to vitamin-D-induced bone mineral mobilization (Duguid, 1930a; L. J. Harris, 1932; Shelling and Asher, 1932). In a 1953 review, Nicolaysen and Eeg-Larsen reported that the dominant feature of hypervitaminosis D is dissolution of formed bone and dense calcification of hypertrophic cartilage.

Duckworth *et al.* (1940), whose magnesium-deficient rats had much less bone

calcification than did those of Orent *et al.* (1934), did not list vitamin D as a dietary constituent. They found that weanling rats, kept on a diet adequate in calcium but low enough in magnesium to result in tetany or convulsions and death by 6 days to a month, had less growth and markedly less magnesium (percent in ash) in their bones than did littermates on the same diet but supplemented with magnesium. In contrast, the magnesium-deficient rats had no decrease (percent in ash) of calcium or phosphorus. In fact, they had a slightly increased percentage of bone ash calcium. Those on the deficient diet for 16 and 23 days exhibited the greatest percentage loss of magnesium as compared to adequately pair-fed rats (0.39 → 0.34% versus 0.83 → 0.74% Mg in bone ash). Rapid replenishment of the bone magnesium was exhibited by rats fed deficient diets for 6 days and then adequate diets for 10 days. The bones of the rats that survived the magnesium-deficient period had more fragile bones than did those reared on adequate rations, and give histologic evidence of abnormal matrix. They then found that rats fed diets deficient in both calcium and magnesium survived longer than did those fed diets adequate in calcium but low in magnesium (Duckworth and Godden, 1941). The rats low in both cations more quickly mobilized more magnesium from their bones, a possible explanation of their longer survival. The rate of bone growth determined the amount of the magnesium that could be liberated because of the demand of the skeleton itself for magnesium. They then showed that when the diet was free of calcium but contained no less than 6 ppm of magnesium, the demineralized bone ash contained progressively more magnesium and less calcium (Duckworth and Godden, 1943). Thus, to a limited extent, the magnesium replaced calcium in the bone crystal. This did not occur with deficiency of both cations.

The mobilization of bone mineral (particularly calcium, the major bone mineral, but also magnesium) by excess vitamin D with low calcium and magnesium intakes or body reserves might be a direct effect, as has been shown with vitamin D metabolites (Trummel *et al.*, 1969; Raisz *et al.*, 1972; Reviews: Norman and Henry, 1974; Norman *et al.*, 1975/1977; DeLuca, 1976) or one that is mediated by secondary hyperparathyroidism. That hypocalcemia causes increased PTH secretion is well established. The effect of hypomagnesemia is neither as well known nor as clear-cut. Larvor *et al.* (1964a) demonstrated that magnesium deficiency (in a calf on normal calcium and vitamin D intakes) caused hyperplasia and osteitis fibrosa. Indirect evidence of increased PTH secretion in rats on diets low in magnesium but adequate in calcium was provided by investigators who prevented hypercalcemia in magnesium-deficient rats by parathyroidectomy (Kukolj *et al.*, 1965; Gitelman *et al.*, 1965, 1968b). I. Clark (1969b) provided evidence that magnesium deficiency in rats fed adequate calcium and phosphate exerts a slight stimulant effect on PTH secretion.

In vitro studies have provided direct evidence of the PTH secretory effect of magnesium deficiency. Perfusion of the parathyroids of goats and sheep (which are separate from their thyroids), with hypomagnesemic, normocalcemic solution resulted in increased PTH secretion (Care *et al.*, 1966; Buckle *et al.*, 1968), an effect that was verified by Sherwood (1970) and his colleagues (Sherwood *et al.*, 1970, 1972; Targovnik *et al.*, 1971). Despite this clear laboratory evidence, severe clinical magnesium deficiency has been shown to cause relative parathyroid failure

(Muldowney *et al.*, 1970; Anast *et al.*, 1972, 1976; Anast, 1977 ; Suh *et al.*, 1971, 1973; L. Chase *et al.*, 1974; Avioli, 1978), an effect that can be mediated by decreased PTH release (Anast, 1977) or skeletal unresponsiveness (Estep *et al.*, 1969; C. Reddy *et al.*, 1973; Levi *et al.*, 1974; Medalle *et al.*, 1973, 1976). However mediated, Forbes and Parker (1976/1980) have shown diminished bone resorption (as measured by ^{45}Ca levels) in magnesium-deficient young rats.

Why a condition associated with increased PTH secretion (that mobilizes bone minerals and leads ultimately to magnesium loss, as well as hypercalcemia) should be associated with increased levels of bone magnesium in the acute studies, is difficult to explain. It is conceivable that the enhancement by PTH of mitochondrial uptake of magnesium (Rassmussen *et al.*, 1964) might be contributory. The increase in bone magnesium, associated with hypervitaminosis D, might be correlated with a possible PTH-mediated early bone uptake of magnesium. Since magnesium participates in osteoblastic activity and osteoid formation, the net result of the imbalance produced by concomitant hypervitaminosis D and low calcium intake (and that causes hypomagnesemia) might well be the high magnesium/calcium bone ratio, and the relative excess of osteoid, such as is seen in clinical rickets and in hyperparathyroidism. It might also include the osteomalacia of malabsorption syndromes and vitamin-D-resistant rickets following high-dosage calcemic therapy.

Possibly the initial response to hypomagnesemia of the CT producing C cells is increased secretion, even in the absence of hypercalcemia (Rojo-Ortega *et al.*, 1971). It is conceivable that this response functions to inhibit release of bone magnesium, as well as to partially counteract the mobilization of bone calcium of animals loaded with vitamin D. However, compensatory CT secretion is insufficient to counteract calcium mobilization from bones of rats given very high doses of vitamin D (Mittleman *et al.*, 1967).

Despite the (possible) increase in CT secretion, hypervitaminosis D (usually in adults whose calcium intake is not high) has caused hypercalcemia and bone demineralization, as well as metastatic calcification.

11.3. High Phosphate Intakes: Effects on Bones

11.3.1. Effects on Bone Magnesium

E. R. Morris and O'Dell and their colleagues studied the influence of increasing the phosphate intake on skeletal and dental structures of guinea pigs on low to normal magnesium intakes, keeping the calcium intake adequate and constant (O'Dell *et al.*, 1960; E. R. Morris and O'Dell, 1961). Although the calcium and phosphorus levels of the hard structures remained essentially the same in magnesium-deficient and control animals, regardless of the intake of phosphate, the animals on a diet low in both magnesium and phosphate had one-third as much magnesium in their bones and teeth as did animals on control magnesium intakes, also low in phosphate. Increasing the phosphate increased the magnesium requirements for survival, and induced changes in bone and tooth minerals (O'Dell *et al.*, 1960). At both the low- and high-phosphate intakes, increasing the magnesium levels 70- and 35-fold, respectively, significantly increased the magnesium levels of the hard

TABLE 11-1. Bone and Tooth Minerals of Guinea Pigs on Constant Calcium[a] Intake as Influenced by Dietary Phosphorus and Magnesium[b]

Diet composition (%)		Bone (%)			Molars (%)			Incisors (%)		
P	Mg	P	Ca	Mg	P	Ca	Mg	P	Ca	Mg
0.4	0.005	11.5	24.3	0.20[c]	14.6	28.8	0.38[c]	14.6	27.3	0.36[c]
0.4	0.34	12.0	24.4	0.60	15.2	27.0	1.33	15.1	26.3	1.18
1.7	0.01	11.3	23.1	0.34[c]	15.4	29.0	0.76[c]	14.8	27.8	0.67[c]
1.7	0.34	11.7	21.8	0.80	15.0	27.0	1.23	15.1	26.0	1.24

[a] 0.09% Ca.
[b] Derived from Morris and O'Dell (1961).
[c] Significantly different from the 0.34% dietary Mg level.

structures (Table 11-1) and prevented their structural defects. The investigators speculated that the phosphate-induced loss of skeletal magnesium caused abnormalities in the matrix. Forbes (1961) evaluated the effects of varying dietary ratios of calcium, magnesium, and phosphorus in weanling rats. He demonstrated that on marginal magnesium intakes, overt magnesium deficiency was produced only when excesses of both calcium and phosphorus were provided. The percentage of magnesium in femur ash was lowest in magnesium-deficient rats supplemented with both calcium and phosphorus and was almost as low when supplemented only with phosphorus (Forbes, 1963).

In studies of the effects of magnesium depletion and repletion on rats depleted of or provided adequate calcium and phosphorus, I. Clark (1966, 1968, 1969a, b,1971/1973, 1977) showed that the amount of each ion required or tolerated is influenced by the intakes of the others (Fig. 11-1). He also showed that femoral weight and calcification is depressed without optimal magnesium intake. In a study of bone minerals in rats on constant calcium and phosphate intakes, but on low-to-high magnesium supplements, Clark and Bélanger (1967) found declining bone calcium and magnesium as the dietary magnesium-to-calcium ratio declined. Meyer and Busse (1976/1980) reported that changing vitamin D intakes did not alter bone-magnesium levels in rats on high phosphorus intakes, although they confirmed that vitamin D slightly lowered blood levels of magnesium. They found that the magnesium-bone content of rats fed diets with slightly higher phosphorus than calcium content was slightly higher than that of rats fed diets with three times as much calcium as phosphorus. In sheep, there was also more magnesium in bone ash than when the dietary calcium to phosphorus ratio was low than when it was high.

11.3.2. High P/Ca; P/Mg and Bone Wasting; Mineralization

11.3.2.1. Bone Wasting

In view of the cited evidence that excess phosphate decreases bone magnesium levels, and the importance of magnesium in maintaining normal bone metabolism, the evidence that experimental high phosphorus/calcium ratios causes bone wasting

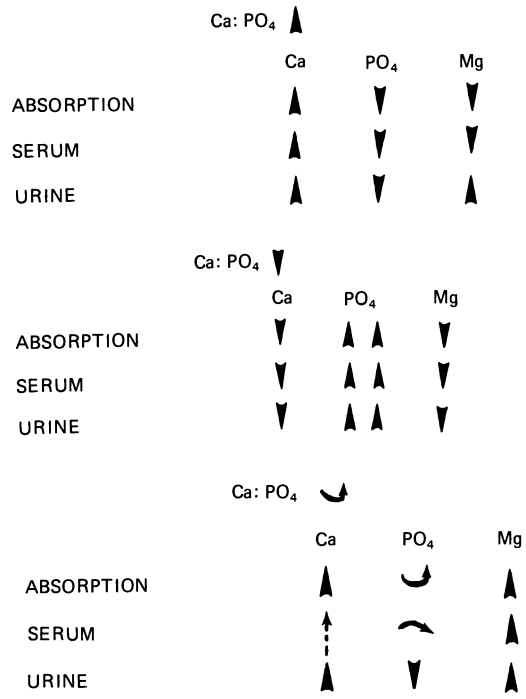

FIGURE 11-1. Effect of increasing dietary calcium, phosphate, or magnesium on absorption, serum and urine Ca, PO_4, and Mg. [from I Clark: *Nutritional Imbalances in Infant and Adult Disease*. MS Seelig (Ed), Spectrum, New York, 1977, pp 43–58.]

is relevant. Data referable specifically to the renal calcinosis produced by diets with high phosphorus/magnesium ratios, or that cause increased phosphorus mobilization, will be discussed in Chapter 13.

Shelling and Asher (1932) studied the influence of different proportions of dietary calcium and phosphorus on bone and soft tissue calcification of rats given no vitamin D, or given moderately high to very high doses. Young rats on high P/Ca dietary ratios developed osteoporosis, which was intensified by increasing the phosphorus intake further, and further worsened by addition of large doses of vitamin D_2. Microscopic studies of young rats on low calcium/high phosphorus and vitamin D (40,000 times the antirachitic dose) showed a progressive decrease in the number of trabeculae with the duration of the experiment. At the end (by the 26th day), the trabeculae had been replaced by remnants of osteoid, osteoblasts, and tiny fragments of calcified material. The similarity of these abnormalities to those seen in the genetic abnormality, hypophosphatasia, and the low alkaline phosphatase levels of infants with hyperreactivity to vitamin D deserves consideration.

More recently, the risk of bone wasting (caused by high P/Ca in the diet) has been studied by Krook *et al.* (1971, 1975). They demonstrated nutritional osteoporosis in dogs, horses, pigs, and monkeys kept on diets with high phosphorus/calcium ratios for prolonged periods of time. The disease is characterized by hypercalcemia and hypophosphatasia; the bone damage, both in long bone and in

mandibles, is related to secondary hyperparathyroidism (attributed both to the low dietary calcium and high dietary phosphate). The histological changes resemble those of osteoporosis, and are characterized by loss of matrix and by demineralization, particularly in the subperiosteal areas of the compact bone. In trabecular bone, osteocytic osteolysis occurs in the center, and the trabeculae become thinner. It is likely that excess phosphate-induced depletion of magnesium contributes to the enzyme, parathyroid, and bone changes.

Feinblatt *et al.* (1970) also observed that high phosphate/calcium ratios (in rats) cause similar lesions. They also demonstrated that phosphate infusions reduced the hypercalcemia caused by PTH administration, but did not alter its increase of urinary hydroxyproline secretion. Thus, their findings indicate that phosphate does not block bone resorption, but they assume that it increases bone mineralization. Comparable osteoporotic changes have been produced by excess dietary phosphate in adult intact and parathyroidectomized rats (G. Anderson and Draper, 1972) and in aging mice (Krishnarao and Draper, 1972) and rats (Draper *et al.*, 1972). Lutwak (1974) has commented that such intakes are common in the American diet, and suggested that they might be contributory to the high frequency of osteoporosis and periodontal disease. In contrast, Berlyne *et al.* (1973b) have attributed the rarity of renal osteodystrophy in Israel to a low phosphorus intake.

11.3.2.2. Bone Mineralization

That phosphate loads might increase bone mineralization was first proposed by F. Albright *et al.* (1932), who speculated that inorganic phosphate's antihypercalcemic effect (in hyperparathyroidism) was mediated by inhibition of bone resorption. Raisz and Niemann (1969) demonstrated this effect *in vitro*, and then showed that increasing the phosphate concentration of suspending media stimulated collagen synthesis by rat bone (Raisz, 1970). However, phosphate loading has stimulated PTH secretion, and failed to inhibit PTH-induced bone resorption, as indicated by continued excretion of bone minerals and hydroxyproline (Pechet *et al.*, 1967; Feinblatt *et al.*, 1970; Rasmussen *et al.*, 1970). Despite its failure to suppress PTH-bone resorption, Pechet *et al.* (1967) reported that the neutral phosphate stimulated bone formation and mineralization. They explained this finding on the basis that considerable amounts of phosphate are bound by collagen and initiate crystal nucleation and growth (Glimcher and Krane, 1964).

11.4. Influence of Metabolic Activity of Bone on Availability of Bone Magnesium

Availability of radioisotopes of magnesium (i.e., ^{28}Mg) has permitted study of the influence of the metabolic activity of bone on its uptake and release of magnesium during short periods of time. Brandt *et al.* (1958) found considerable variability in skeletal ^{28}Mg uptake by different bones of different dogs, and postulated that the rate of uptake is likely to be affected by many factors: growth, renal function, and the magnesium stores of the body. A. C. Field (1960) found that there was

TABLE11-2. Uptake of ^{28}Mg by Compact versus Largely Cancellous Bone of Sheep[a]

Bone	Specific activity	
	% of Mg dose ($\times 10^2$/mg Mg)	% of specific activity in plasma
Femur (shaft)	0.048	0.86
Femur (epiphysis)	0.130	2.3
Rib (shaft)	0.079	1.4
Rib (sternal end)	10.129	2.3
Lumbar vertebra	0.099	1.7

[a]From data in A C Field (1960).

marked variation in magnesium uptake from bone to bone in sheep. It was greater in regions of rapid bone metabolism than in compact bone (Table 11-2). Using a radiographic procedure to measure the uptake of ^{28}Mg in puppies, Glaser and Gibbs (1962) showed that the growing, actively metabolizing portion of bone (the epiphyseal line) concentrates most of the ^{28}Mg that is taken up by bone, as compared with the diaphysis, the least active portion.

In a study comparing predominantly the influence of age on the amount of magnesium mobilized from bone of magnesium-deficient rats (B. S. W. Smith and Field, 1963), there was relatively more magnesium lost per unit of mandible than per unit of femur. More magnesium was lost from the bones of the young rats (mandibular versus femoral magnesium loss = 33.3% versus 28.2%), but proportionally more was lost from the mandibles of the older rats (13.4% versus 9.5%). Parr (1957) confirmed the greater loss of magnesium from cancellous than from compact bone of magnesium-low calves. McAleese (1961) showed that epiphyses of magnesium lambs took up more ^{28}Mg than did the diaphyses, indicating either more magnesium loss from the area of bone growth, its greater magnesium requirement, or both.

In a serial study of loss of magnesium from vertebrae, R. H. Smith (1959) amputated the terminal caudal vertebra at monthly intervals from magnesium-deficient and control calves, and found that the magnesium content of the bone ash dropped before the appearance of clinical signs of deficiency. Larvor *et al.* (1964a) showed that the diaphyses of magnesium-deficient calves lost less magnesium (compared with controls) than did the vertebrae. The ratio of vertebral magnesium in deficient versus control calves was 0.16:0.35; that of diaphyseal magnesium was 0.25:0.41. There was very little difference in bone calcium or phosphorus in the magnesium-deficient and control calves. B. S. W. Smith and Field (1963) found that magnesium-deficient rats lost relatively more magnesium from mandibular than from femoral bone. Minimal osteoblastic and alkaline phosphatase activity was found in alveolar bone of magnesium deficient rats (Trowbridge and Seltzer, 1967).

Aikawa (1965) demonstrated that the rate of bone uptake of ^{28}Mg is influenced by the metabolic activity of the bone cells. Administration of insulin and glucose (Aikawa, 1960a) or of pyridoxine (Aikawa, 1960c) increased the bone uptake of

^{28}Mg; inhibitors of thyroid function of pyridoxine activity, or irradiation, decreased bone ^{28}Mg uptake (Aikawa, 1960b; Aikawa and Reardon, 1963; Aikawa, 1965). MacManus and Heaton (1970) demonstrated that, *in vitro,* metabolically active bones release more magnesium to a magnesium-free medium than do bones whose enzymatic activity has been destroyed by aging. Heaton (1971) thus concludes that magnesium is released by a mechanism that is dependent on the metabolic activity of bone cells. (In the *in vitro* system, most of the magnesium released reflects establishment of a physicochemical equilibrium between the bone and its surrounding fluid.)

Bones with a high proportion of cancellous to compact bone (more metabolically active) develop clinically manifest osteopenia before predominantly compact (long) bones do. Thus, the greater loss of magnesium from such bones, relatively early in magnesium deficiency, might be clinically important, in view of magnesium's significance in so many enzyme systems (Reviews: Lehninger, 1950; Green and MacLennan, 1960; Heaton, 1976/1980). The intensification of magnesium deficiency by calcemic agents and phosphates, such as are commonly used in treatment of osteopenias and hypercalcemic states, might intensify bone matrix abnormalities and lead to the formation of hypermineralized bones with little matrix. It is possible such bones are similar to the brittle chalky bones and teeth seen in magnesium-deficient rats fed diets high in calcium, phosphate, and vitamin D_2. Animals fed magnesium-deficient rations more similar to the human diet (high P/Mg and P/Ca) ratios tend to develop osteopenia. Rarely is the possibility that calcemic treatment of clinical osteopenias might intensify magnesium deficiency considered (Amiot *et al.,* 1969; Durlach, 1971).

11.5. Influence of Age on Mobilization of Bone Magnesium

That skeletal magnesium is not readily mobilized in adult animals was suggested by the early work of Cunningham (1936a), who showed that bones from lactating cows with grass tetany and hypomagnesemia contained normal amounts of magnesium. Calves, however, kept on a diet low enough in magnesium (Mg/Ca=¼) to cause convulsions or death in 8 to 16 days, lost about two-thirds of their bone magnesium (Blaxter *et al.,* 1954). Blaxter (1956) later evaluated the tissue magnesium changes in magnesium-deficient calves and found that soft tissue levels were not significantly depleted, but that there was a 56% loss of bone magnesium. His data suggested that the loss of skeletal magnesium takes place at the surface of the bone crystals, and that it occurs more readily in young than in old animals. Less severely depleted calves lost less bone magnesium, but more than did cows with lactation tetany (Parr, 1957), a condition associated with magnesium depletion.

In the case of rats, which continue to grow after they reach sexual maturity, the results are generally not as clear-cut. Breibart *et al.* (1960) found that young rats (20 to 30 days of age:44–100 g) exchanged 31–46% of their bone magnesium with ^{28}Mg, whereas 60 to 180 day-old rats (130–225 g) exchanged only 4–5% of bone magnesium. Young rats (90–110 g) that were kept on a magnesium-deficient diet

high in calcium (Mg/Ca = 3.8/1500 mg/100 g diet) that maintained their growth, but at 1/6 the control rate, showed a pattern of distribution of injected ^{28}Mg different from controls (Chutkow, 1965). Initially (within 3 minutes after the injection) there was prompt uptake of greater amounts of ^{28}Mg (than in controls) by all tissues, including bone. Thereafter, most of the ^{28}Mg was diverted to the soft tissues; the skeletal uptake of ^{28}Mg did not exceed that achieved during the first few minutes. The study of A. C. Field and Smith (1964) was on the effect of magnesium deficiency on the uptake of ^{28}Mg by mature rats (9–12 months old; averaging 400 g in weight), but cannot be directly compared with the Chutkow study (1965) because the Mg/Ca ratio was much lower: $CaCO_3$: 75 parts, versus hydrated $MgSO_4$: 26 parts in controls, and absent from deficiency diets. They (Field and Smith) found that the bones of magnesium deficient rats took up less ^{28}Mg than did the viscera (versus controls). The mandible took up relatively more magnesium than did the femur, the uptake of which was about equal to that of skeletal muscle. The relative specific activities (the ratio of that of the tissue to that of plasma, a measure of the proportions of exchangeable magnesium) of bone from the magnesium-deficient adult rats were less than in control rats, in contrast to the relative specific activities of the vital organs.

B. S. W. Smith and Field (1963) compared the amount of magnesium mobilized from the bones of 8-week-old male and female magnesium-deficient rats (180 and 140 g) with that from 9- to 12-month-old males (average weight: 400 g). They found that the young rats lost much more bone magnesium than did the old rats. The femurs of the magnesium-deficient young rats showed 28.2% magnesium depletion from femurs, as compared with controls; the mandibles showed somewhat more: 33.3% magnesium depletion versus controls. There was less loss of magnesium from the adult rats: 9.5% depletion in femurs; 13.4% depletion in mandibles versus controls. Martindale and Heaton (1964), however, found that mature rats, 4 to 5 months of age, lost bone magnesium rapidly during the first 15 days of deficiency, and then more slowly to reach about half the starting value after 62 days. The pattern of change was similar to that seen in blood plasma. These rats showed a significant rise in bone content of calcium and sodium, a finding in accord with the early studies (Orent *et al.*, 1934), in which rats were given rations high in calcium. [Note that most magnesium-deficient rat diets are high in calcium, phosphate, and vitamin D (Review: Larvor and Durlach, 1971b).]

11.6. Physicochemical Exchange of Bone Magnesium and Calcium

The hypocalcemia of severe magnesium depletion, which has been attributed to target organ unresponsiveness to PTH (or to failure of PTH release or secretion), has been explained by physicochemical factors involving ionic exchange of magnesium and calcium at the bone surface. Heaton (1971) has reviewed the evidence that bone magnesium is much more readily available than is bone calcium. (About a third occurs within the apatite crystals, the remainder being either adsorbed on the crystal surface or present in solution within the hydration shell around the crystals.)

Duckworth and Godden (1941) showed that calcium exchanges for magnesium in the apatite crystal during magnesium depletion. Neuman and Neuman (1957) suggested that calcium ions can enter the extracellular fluid from bone only if the bone crystal takes up other cations (i.e., magnesium) to maintain electroneutrality. R. H. Smith (1961) speculated that the correlation of falls in plasma magnesium and calcium in magnesium-deficient calves might affect the availability of bone calcium. He observed that the fall in bone magnesium levels reflects that of serum magnesium, and that thus there is less extracellular magnesium available for exchange with calcium. Zimmet (1968) considered this possibility in interpreting the hypocalcemia of his magnesium-depleted patients, noting that Heaton and Fourman (1965) had suggested that magnesium deficiency interferes with release of calcium from bone. Larvor *et al.* (1964) showed that, during the early stage of magnesium deficiency in the calf, there is a slowing of the rate at which skeletal calcium exchanges with that in the blood. The postulate of Neuman and Neuman (1957) was proved when it was shown that addition of magnesium to an incubation medium increases the release of calcium from bone (Pak and Diller, 1969; MacManus and Heaton, 1970). The magnesium-induced release of calcium is accompanied by liberation of hydroxyproline (MacManus and Heaton, 1970), suggesting that magnesium is involved in bone turnover (Heaton, 1971).

11.7. Alkaline and Pyrophosphatases, Magnesium, and Mineralization of Bone

11.7.1. Magnesium Requirement for Phosphatase Activation and Synthesis

In a 1950 review, Lehninger reported that virtually all phosphatases or phosphate-transferring enzymes are activated by magnesium. As early as 1931, Von Euler and Rydbom found that magnesium, fed to rats on a rachitic diet, increased their subnormal serum phosphatase levels. Snyder and Tweedy (1942) reported that severe experimental magnesium deficiency causes reduced serum alkaline phosphatase activity, an effect that has been verified in cattle and rodents (Larvor *et al.*, 1964a; Heaton, 1965; Pimstone *et al.*, 1966; Trowbridge and Seltzer, 1967; B. Smith and Nisbet, 1968; Hamuro, 1971; Elin *et al.*, 1971b; Loveless and Heaton, 1976). The observations that serum and skeletal alkaline phosphatase levels are low in acutely magnesium-deficient rats, and that addition of exogenous magnesium to the medium does not raise the enzyme level to that found in tissues of control rats, indicate that magnesium deficiency reduces the amount of phosphatase present, and not just its activity (Loveless and Heaton, 1976). Low bone levels of alkaline phosphatase have also been found in acutely magnesium-deficient rats by Trowbridge and Seltzer (1967) and Lai *et al.* (1975). Subacute magnesium deficiency in rats did not cause lowering of bone or serum alkaline phosphatase (Watchorn and McCance, 1937).

In a long-term magnesium depletion study (in patients who had undergone radical face and neck surgery for cancer), serum alkaline phosphatase levels gradually

declined (to 1–2 Bodansky units) and did not increase with magnesium supplementation until the 56th day of repletion (Shils, 1969a). A shorter (1 month) study of healthy young men on a low-magnesium diet showed no reduction in serum alkaline phosphatase, even though their magnesium deficit was demonstrable by retention of large amounts of magnesium during repletion (Dunn and Walser, 1966). These volunteers did not develop hypomagnesemia; it seems likely that their bone stores of magnesium were sufficient to prevent interference with serum alkaline phosphatase activity. Possibly masking a (presumed) decrease in enzyme synthesis might be mobilization of alkaline phosphatase from the bone, to a lesser degree than that seen in neoplastic and bone diseases (Taswell and Jeffers, 1963; Moses and Spencer, 1963).

Low serum alkaline phosphatase activity was demonstrated in children with protein calorie malnutrition (R. Schwartz, 1956), a condition in which magnesium depletion has been identified. R. Schwartz (1956) has proposed that the very low serum alkaline phosphatase activity of such children can be correlated with decreased osteoblastic activity. Addition of magnesium to their serum increased the enzymatic activity, but not to the level found in normal children, an effect similar to that reported in studies of magnesium-deficient rats (Heaton 1965; Pimstone *et al.*, 1966).

Low levels of serum alkaline phosphatase have also been found in adults with severe, long-term magnesium depletion (Hanna *et al.*, 1960; Hanna, 1961b; Zimmet *et al.*, 1968; Sutton, 1968; Muldowney *et al.*, 1970; T. B. Connor *et al.*, 1972), and have risen with magnesium infusions (Zimmet *et al.*, 1968). They have also been reported in infants with hypercalcemia related to hypervitaminosis D and in other conditions associated with hypercalcemia (N. J. David *et al.*, 1962). Since both excess vitamin D and calcium predispose to magnesium deficiency, the low alkaline phosphatase levels found in such patients might reflect a conditioned magnesium deficiency. Patients with bone involvement of neoplastic disease (who had hypercalcemia) had lower alkaline phosphatase levels than did those with normocalcemia (Moses and Spencer, 1963). In fact, the hypercalcemia preceded the lowering of enzyme levels (Griboff *et al.*, 1954), possibly a reflection of calcium inhibition of phosphatase.

The genetic bone disorders associated with hypophosphatasia, and in which abnormal magnesium metabolism might play a role, are discussed elsewhere. One such disease, osteosclerosis, which is seen in infantile hypercalcemia [associated with hyperreactivity to vitamin D (Review: Seelig, 1969b) has been duplicated in pigs given 5 to 25 the antirachitic dose of vitamin D (Chinemene *et al.*, 1976)]. On higher doses, the pigs developed hypophosphatasia. The few studies of magnesium in infants with the established syndrome have yielded conflicting results. However, one valuable study has been found that provides evidence suggestive of magnesium malabsorption in an infant with osteopetrosis, who had biochemical findings of hypophosphatemic rickets before high-dosage vitamin D therapy had been started, and whose alkaline phosphatase levels dropped from high to low during the eight months of vitamin D therapy (Pincus *et al.*, 1947). A woman with magnesium-deficient latent tetany and rapidly progressive osteoporosis (Seelig *et al.*, 1975), which was found due to renal magnesium wasting (Seelig *et al.*, 1978), exhibited a sharp

drop in her serum alkaline phosphatase following a period of supplementation with 25-OH-D_3, during which her serum magnesium level fell further (unpublished data).

Another nutritional imbalance that has caused hypophosphatasia in several species, in association with hypercalcemia, is a normal calcium intake with three to four times as much phosphorus or more (Krook *et al.*, 1975). This diet is considered one that causes nutritional secondary hyperparathyroidism and that is associated with progressive osteopenia. Not considered as a factor in this model is the magnesium deficit that is produced by phosphate loading. It is conceivable that the secondary hyperparathyroidism, the osteopenia, and the hypophosphatasia might all reflect magnesium depletion. Hamuro (1971) reported that on the first day of a high-phosphate, low-magnesium diet there was a slight increase in serum alkaline phosphatase levels in genetically diabetic mice. By days 4 to 6, the enzyme levels dropped to half the initial value. This decrease was not seen when the diet was supplemented with magnesium or when the phosphorus intake was reduced.

Pyrophosphatase, which also has an absolute and relatively high magnesium requirement (Nagana *et al.*, 1955; Kunitz and Robbins, 1966) was studied in erythrocytes of magnesium-deficient rats (Elin *et al.*, 1971b). It took two weeks of a diet low in magnesium for red cell pyrophosphatase to drop and two weeks of repletion for it to return to control values. The serum alkaline phosphatase levels dropped more rapidly with magnesium deficiency and responded more quickly with repletion. The authors commented that the delay in pyrophosphatase response to magnesium deficiency and repletion is consistent with the slow fall in erythrocyte magnesium levels with its deficiency (Tufts and Greenberg, 1937) and the evidence that the amount of magnesium in the red cells reflects the magnesium status during their formation (Ginsberg *et al.*, 1962). Heaton (1978) has surveyed the interrelations of magnesium with alkaline phosphatase, pyrophosphatase, and orthophosphatase activities. He has considered the controversy as to whether magnesium inhibits or activates pyrophosphatase activity and concluded that the experimental conditions influence the response of the enzymes to magnesium. The general view is now that magnesium stimulates the hydrolysis of pyrophosphate under normal conditions.

It is difficult to obtain precise data as to phosphatase levels, clinically, since the clinical chemistry laboratories report a single serum alkaline phosphatase figure, not distinguishing between that of skeletal and other (e.g., hepatic) origin. Several fractions have been differentiated (Keiding, 1959; Taswell and Jeffers, 1963). Where there is a disease that is likely to cause magnesium loss, and thus abnormal skeletal alkaline phosphatase activity, the high hepatic alkaline phosphatase values that derive from hepatic damage would obscure skeletal hypophosphatasia. Only research laboratories provide data on the differential alkaline phosphatase levels, and only rarely are pyrophosphatase levels obtained.

11.7.2. Alkaline Phosphatase and Skeletal Mineralization

Robison (1923) postulated that bone alkaline phosphatase liberates inorganic phosphate from organic phosphates, with resultant localized increase in phosphate, which then precipitates the calcium. The *in vitro* studies that show that considerable amounts of phosphate are bound by collagen and initiate calcium crystallization

(Glimcher and Krane, 1964) support the premise that interaction of phosphate with collagen plays a role in bone mineralization (Pechet *et al.*, 1967). During bone growth and during osteolytic processes, the serum alkaline phosphatase activity increases (Griboff *et al.*, 1954; Keiding, 1959). Possibly during new bone formation this reflects increased enzyme synthesis; during bone breakdown it might reflect increased enzyme release. On the other hand, both organic and inorganic polyphosphates inhibit calcium phosphate nucleation and precipitation (in collagen or bone matrix). Without an optimal amount of alkaline phosphatase to destroy the inhibitor, bone mineralization is impeded (Fleisch and Newman, 1961, Fleisch and Bisaz, 1962a,b). Subnormal synthesis or activation of enzymes that act to increase the mineralization process, by removing polyphosphate or pyrophosphate inhibitors, can be correlated with clinical conditions associated with abnormal bone formation and low phosphate levels. The most obvious condition is the uncommon genetic defect, hypophosphatasia, in which the magnesium status has not been explored, but that is characterized by unexplained convulsions in infancy not unlike those of hypomagnesemia, with and without hypocalcemia.

The abnormal high pyrophosphate levels found in serum and bone of infants and children with osteogenesis imperfecta, and the *in vitro* lowering of their bone biopsies' pyrophosphate content by addition of pyrophosphatase and magnesium suggest that skeletal hypopyrophosphatasia is likely to be an important factor in this disorder. The lowering of serum and urine pyrophosphates of such patients, with magnesium therapy, suggests that abnormal magnesium metabolism (possibly magnesium malabsorption or wasting) might be contributory.

Patients with bone disease, characterized by increased bone turnover (metastatic malignancy, hyperparathyroidism, hyperthyroidism, and Paget's disease) have all exhibited significantly increased urinary outputs of pyrophosphates, as well as of hydroxyproline. This increased pyrophosphate output might be an index of the amount of bone "metabolized" daily (Avioli *et al.*, 1965). Considering this finding and the preliminary evidence that pyrophosphatase might be part of a control mechanism in both formation and resorption of bone, Tenenhouse and Rasmussen (1968) studied its activity in cell suspensions at a fixed physiologic magnesium concentration, at physiologic pH, and as influenced by PTH and CT. They found that PTH inhibits pyrophosphatase activity, and that CT reverses the inhibitory effect of PTH, effects that they considered to be mediated in part by altering the extracellular ionic environment. Orimo *et al.* (1970) demonstrated that CT administration to rats rapidly increases alkaline pyrophosphatase activity of bone, and suggested that it stimulates bone formation by removing the inhibiting pyrophosphate. These observations should be considered in light of the influence of magnesium on the secretion of both hormones, and on the response of target organs such as bone. It should be kept in mind here that the effects of magnesium deficiency on the hormones and bone depend on the duration and extent of the deficiency. Acute short-term magnesium deficiency increases PTH secretion. Long-term chronic deficiency decreases PTH release and bone response. High-dosage magnesium suppresses PTH secretion. The secretion of CT [which increases osteoblastic activity and decreases bone mineral mobilization (Review: S. P. Nielsen, 1974)] is stimulated by a low magnesium/calcium dietary ratio (Stachura and Pearse, 1970; Rojo-Ortega *et*

al., 1971/1973) and by increased magnesium levels *in vitro* (Radde *et al.,* 1968, 1970) and *in vivo* (Care *et al.,* 1971; S. P. Nielsen 1971/1973; S. P. Nielsen and Jorgensen, 1972; Littledike and Arnaud, 1971).

Increased alkaline phosphatase activity has been demonstrated in the hyperplastic membrane of the thickened diaphysis and subperiosteal proliferation of magnesium-deficient rats (Bélanger *et al.,* 1972), which also showed the more typical epiphyseal growth suppression. This observation supports the premise that the high level of the enzyme lowers that of the inhibiting polyphosphates, allowing for increased mineralization of the diaphysis. Why this magnesium-dependent enzyme should be found in such high concentrations in the membrane of the bone shaft of magnesium-deficient animals requires resolution. Similarly, more study is needed into why the increase in bone shaft alkaline phosphatase of magnesium deficiency should be associated with hyperplasia, resembling desmoid tumors, that was characterized by more fibrous tissue in parathyroidectomized animals, more bone formation when PTH was given, and less subperiosteal hyperplasia when estradiol (an alkaline phosphatase stimulator: Malinow *et al.,* 1960) was given. Another puzzling observation is the association of osteogenic sarcomas with beryllium, which inactivates alkaline phosphatase, possibly replacing the activating magnesium (Grier *et al.,* 1949; Aldridge, 1950).

The bits of evidence that patients with genetic bone dysplasia have abnormal (usually low) bone phosphatase levels, and that low magnesium levels lead to abnormal matrix formation and to defective osteocytic differentiation, suggest that normal magnesium utilization might be at fault. Evaluation of the magnesium status and bone phosphatase levels and activity of patients with genetic or neoplastic bone disease, and of the effect of magnesium on the enzyme activity of the biopsies, might prove worthwhile. If it would lead to prophylactic or therapeutic approaches remains to be seen.

12
Abnormal Bone in Magnesium Deficiency

Bone-wasting diseases that are resistant to physiologic doses of vitamin D, calcium, or phosphate and that have been treated with pharmacologic doses of each or of combinations of mineralizing agents, are likely to be associated with magnesium deficiency. In some instances, initial magnesium inadequacy might be contributory to the osteopenia, as in hyperparathyroidism, secondary to malabsorption, with hemodialysis with low-magnesium water, or possibly in pregnancy. There is suggestive evidence that severe magnesium depletion *(in utero)*, alone or with hypervitaminosis D, might participate in abnormal fetal bone formation that might find expression as fractures of low-birth-weight infants, osteogenesis imperfecta, or hypophosphatasia. In infancy and later in life, vitamin-D- or parathyroid-refractory osteomalacia or hypocalcemia might also have magnesium depletion as a contributory factor. Failure to correct the magnesium deficiency before use of calcemic therapy has failed to correct hypocalcemia. In those with osteopenia (to which magnesium deficiency has contributed), failure to correct that deficit before starting aggressive mineralizing therapy intensifies the imbalance.

Apart from the risk of thereby increasing the risk of extraskeletal damage and calcinosis, such treatment can adversely influence the skeletal system. It can lead to hypermineralization of bone or abnormal matrix, in some instances with exuberant osteoid formation. Marbleized or chalky brittle bones (such as have been described in rats on diets rich in calcium, phosphate, and vitamin D, and poor in magnesium) might develop. If the diet is high in phosphate but poor in calcium and magnesium, osteopenia has been seen. Low magnesium intakes, when severe, have been associated with desmoidlike tumors; whether the abnormal osteoid at sites of pseudofractures is a disorder of common etiology remains to be determined. It is provocative that severe magnesium depletion is most commonly recognized with vitamin-D- or PTH-refractory hypocalcemia, usually without bone wasting.

12.1. Osteopenia of Magnesium Deficiency (Animals)

It has long been known that magnesium-deficient animals have arrested growth (Leroy, 1926; Kruse *et al.*, 1932), but the precise nature of the bone abnormalities produced has not received much attention. In 1930, Huffman *et al.* reported that the ribs of magnesium-deficient calves are easily broken at the sternal ends, and that the specific gravity of the long bones is subnormal. Cunningham (1933) reported that rats on diets low in magnesium have narrowed epiphyseal plates, which contain few chondrocytes, and that the subepiphyseal region has few trabeculae. Duckworth *et al.* (1940) noted the fragility of the long bones of their magnesium-deficient rats and attributed it to abnormal matrix. Yamane and Singer (1953) observed that metaphyseal bony trabeculae are lost and that the zone of preliminary calcification just below the epiphysis is atrophic or absent in magnesium-deficient hamsters. Blaxter (1956), who found no histological evidence of abnormality of the calcification process in bones of acutely magnesium deficient calves, speculated that the matrix might be adversely affected. E. R. Morris and O'Dell (1961) postulated that magnesium deficiency interferes with cellular function of hard tissues, thereby preventing formation of normal matrix.

Since then, firm evidence has been obtained that magnesium deficiency does, in fact, interfere with normal formation of the matrix of both bones and teeth. Bernick and Hungerford (1965) found differences in staining characteristics that suggested that the ground substance of the magnesium-deficient matrix contains mucopolysaccharides that are less polymerized and less subject to normal calcification. They also compared the histologic differences between the epiphyses of the rats fed a magnesium-deficient diet for 19 days, and those of controls. They confirmed the early evidence that the cartilage of the epiphyseal plate of the heads of the tibias of the deficient rats is slightly narrower than normal. They found trabeculae, extending from the metaphysis into the diaphysis, that are shorter and wider than normal. The proximal epiphyseal cartilages of the deficient rats exhibit a slight decrease in number of proliferating cells, and relative increase in the number of hypertrophied cells, and a decrease in the width of the calcifying matrix. Clark and Bélanger (1967) also showed thinner epiphyseal plates in magnesium-deficient rats, and few chondrocytes. There were practically no new trabeculae at the subepiphyseal area, and the diaphysis contained immature matrix with small elongated osteocytes. This was confirmed in later studies (Hunt and Bélanger, 1972; Bogoroch and Bélanger, 1975).

Trowbridge and Seltzer (1967) investigated the effect of acute magnesium deficiency on the organic matrix of bone and dentin employing the uptake and tritiated proline to assess collagen formation, $^{35}SO_4$ to assess sulfation of protein polysaccharides, and measuring the biochemical localization of alkaline phosphatase in bones and dentin. They found minimal osteoblastic activity, with marked suppression of the amount of tritiated proline uptake in the collagen of the bone matrix in the deficient rats. Also, sulfation of glycosaminoglycuronoglycans was diminished in the osteogenic layer of the periodontal ligament, and reduced intensity of staining for alkaline phosphatase in the periodontal ligament and in osteoblasts suggests that magnesium deficiency decreases bone alkaline phosphatase; serum levels of the enzyme were also low. Hunt and Bélanger (1972) also showed that the cartilage

matrix of magnesium-deficient rats appeared depleted in sulfated mucopolysaccharides. The underlying bone spicules of the epiphyseal plate of the tibia were thin and poorly ossified, as were the diaphyses.

Lai *et al.* (1975) have verified the reduction in bone magnesium, phosphatase, and matrix in magnesium-deficient rats and found hypermineralization with increased bone ash and calcium content. Their findings were more similar to those of Orent *et al.* (1934) and Watchorn and McCance (1937) than they were to those of Duckworth *et al.* (1940). The former two groups had fed their rats diets high in calcium and vitamin D; the latter used less calcium and did not indicate use of vitamin D. [Lai *et al.* (1975) did not specify the nature of the basic diet, but basic rat diets, provided currently from most firms, are rich in calcium, phosphorus, and vitamin D.] The bones were more brittle than those of control rats.

Bone matrix implanted in skeletal muscle of magnesium-deficient rats, and controls fed the same commercially supplied deficient diets, but supplemented with 265 mg/100 g of diet showed marked differences in bone growth and development (Bélanger and Robichon, 1975). There was osteoporosis in the lumbar vertebrae of the magnesium-deficient rats, and very little bone formed on either the inside or the outside of the implants. Only 2 of the 15 rats that survived 3 weeks formed new trabeculae, and these were fibrillar and poorly mineralized. At several sites, there were small amounts of bone tissue mixed with islands of chondrocytes, surrounded by precartilaginous or poorly differentiated matrix. Further outward from the implant there was an "envelope" of fibroblastlike cells and collagen that separated the implant from the muscle. In half of the specimens, there was invasion of the implant by thin cartilage wedges, coming mostly from the periphery of the implant. Near these wedges, there was deterioration of the implant matrix. In contrast, the magnesium-supplemented rats had formed well-mineralized trabecular bone inside and outside the implant. In a few areas, cartilage or a mixture of cartilage and bone had formed.

12.2. Abnormal Bone: Hypermineralization and Hyperplasia of Magnesium Deficiency

Paradoxically, magnesium-deficient animals have exhibited excess (abnormal) bone growth in addition to osteopenia. Generalized medullary bone growth (osteomyosclerosis) and periosteal tumors of the desmoid type occurred at the femoral linea asperea in severely magnesium-deficient rats (Bélanger and Hunt, 1971/1973; Hunt and Bélanger, 1972). (This is a prominent longitudinal ridge on the middle third of the bone, with rich vascular supply, and concomitant sites of accretion and osteocytic osteolysis, which indicate that it is an area of considerable metabolic activity.) The degree of magnesium deficiency was critical in the formation of both the periosteal tumors and intramedullary bone; both abnormalities were produced only in severely magnesium-deficient rats, but irrespective of the concentration of bone magnesium. The investigators speculated that matrix and bone cells could be differentially depleted of magnesium, and that the bony overgrowth was related to changes in the magnesium concentration in the organic phase of bone. The perios-

teal tumors rapidly disappeared when the rats were supplemented with magnesium. This was interpreted as indicative of magnesium depletion-induced accumulation of cells unable to differentiate properly, possibly as a result of enzymic malfunction. Deficient rats that developed fibrous hyperplasia showed high concentration of alkaline phosphatase activity throughout the hyperplastic membrane (Bélanger *et al.*, 1972a).

Although the periosteal desmoid tumor was first shown to be a characteristic of magnesium deficiency by this group (Hunt and Bélanger, 1972), the authors noted that Duckworth *et al.* (1940) had referred to "disordered growth of the organic matrix of leg bones" in their magnesium-deficient rats that might have been a comparable phenomenon. Lai *et al.* (1975) later observed that 10 of their 11 magnesium-deficient rats had tumorlike femoral exostoses.

These tumorlike growths resemble that described by McCance (1946) in an adolescent girl who developed weakness and hypophosphatemic vitamin-D-resistant osteomalacia at the age of 15. She had multiple spontaneous pseudofractures and callus formation of her long bones (Looser's nodes), and had a tumor on the shaft of the tumor. Histologic examination showed abnormal osteoid tissue that was not considered neoplastic. Metabolic balance studies, done while the patient was receiving about 2000 units of vitamin D daily, showed substantially negative balances of calcium, phosphorus, and magnesium. On a daily magnesium intake of about 230 mg, she lost an average of 25 mg/day over a 7-day period. Massive vitamin D therapy (500,000 units/day) greatly improved her retention of calcium and phosphorus but improved the magnesium retention only slightly. The vitamin D was stopped when signs of toxicity developed (after a month), and her magnesium retention improved markedly (to +40 mg/day). When her magnesium intake was increased (to 390 mg/day) she went into strongly positive magnesium balance (+90 mg/day) and showed steady clinical improvement.

It is provocative that similar exostoses, described as irregular subperiosteal new bone formation or exuberant callus, have been reported in patients with hypophosphatasia (Schlesinger *et al.*, 1955; Currarino *et al.*, 1957), a condition postulated to be related to magnesium depletion. Hypophosphatemic rickets has also been associated with profound weakness and Looser's nodes in an adult, who also had a lengthened QT interval (Milne *et al.*, 1952). The authors attributed the weakness and abnormal ECG to her hyperkalemia. The bone and cardiac manifestations might also have had magnesium deficiency as a common cause.

Hunt and Bélanger (1972) found that parathyroid activity influenced the nature of the bone tumor produced by experimental magnesium deficiency. Parathyroidectomized magnesium-deficient rats had a large tumoral mass that consisted of layers of fibrous tissue on the outside, then cartilage, and an internal layer of bone. Administration of PTH to these animals reduced the amount of cartilage, which then appeared as small peripheral isolated units, and resulted in abundant growth of medullary bone throughout the central cavity of the femur and tibia. In view of the estrogen/PTH antagonism in bone accretion and resorption (Ranny, 1959; Review: Seelig and Lehr, 1971/1973), the observation that ovariectomy, with and without estradiol administration, modified the incidence and severity of skeletal lesions caused by magnesium deficiency (Bogoroch and Bélanger, 1975) is provocative.

Although the reduction in diaphyseal width of magnesium-deficient ovariectomized rats did not differ significantly from that seen in intact deficient rats, some of the ovariectomized rats showed greater subperiosteal hyperplasia. Estradiol-treated magnesium-deficient rats had a quarter the incidence of subperiosteal hyperplasia seen in untreated magnesium-deficient rats. Possibly related is the fourfold increase in plasma alkaline phosphatase activity produced by estradiol treatment of chickens (Malinow *et al.*, 1960), since alkaline phosphatase synthesis and activity are magnesium dependent and the enzyme is involved in bone metabolism.

Bone tumors have also been experimentally produced by beryllium (Janes and McCall, 1975), which inhibits alkaline phosphatase, an inhibition that is partially reversed by adding magnesium (Aldridge, 1950; Grier *et al.*, 1949). It is thus of interest that both in human and experimental osteogenic sarcoma, magnesium bone tumor levels were low (Janes *et al.*, 1972; Jones and McCall, 1975). This brings us to the discussion by Hunt and Bélanger (1972) of the significance of their observation of the osteomyelosclerosis and subperiosteal tumors of their magnesium-deficient rats. They noted that the deficiency-induced lesion seemed to correspond to the periosteal desmoid described in the *Catalogue of Tumors of Bone and Cartilage* (Spjut *et al.*, 1969), which is described as midway "between a true tumor and nontumorous connective tissue hyperplasia." They also noted that the occurrence of osteomyelosclerosis occurs in human disease, frequently in association with certain forms of leukemia and other blood dyscrasias and that leukemia has occurred in magnesium-deficient rats (McCreary *et al.*, 1967; Battifora *et al.*, 1968).

Thus, magnesium deficiency causes major metabolic disturbances of the bone that can lead to osteopenic yet hypermineralized brittle bones as well as hyperplasia and might even participate in an early neoplastic process. The degree of the deficiency as well as the concomitant dietary imbalance and hormonal responses, affects the nature of the lesion produced. Possibly much of its direct effect on bone is mediated by its effect on synthesis or activation of phosphatases, by its effects on bone matrix, and by its influence on differentiation of the bone cells.

12.3. Bone Diseases Possibly Related to Magnesium Deficiency

12.3.1. Fetal Magnesium Deficiency and Bone Damage

12.3.1.1. Interrelationships with Parathyroid Hormone and Calcitonin

The failure of maintenance of fetal magnesium levels at the expense of the mother can result in responses in PTH and CT secretion that can influence fetal bone growth and development. Both the parathyroids and the C cells are functional early in fetal life. They are influenced by the maternal magnesium and calcium levels, both of which have been shown to have a tendency to be low. Both cations, unlike PTH and CT, can cross the placental barrier, and thus must be controlled by fetal parathyroid and C-cell responses. This homeostatic control is mediated by

their effects on fetal bone. Fetal rat bone, kept in a medium low in magnesium (0.3 mM), showed less release of tagged calcium when exposed to PTH (Raisz and Niemann, 1969), an effect like that seen in the intact magnesium-deficient experimental animal or human. Fetal bones in media high in magnesium (4.3 mM) showed the same release of calcium from bone as did bones kept in physiologic magnesium and calcium concentrations when PTH was added. Bone resorptive activity of human fetal parathyroids has been demonstrated as early as 12 weeks gestation, at which time there are secretory granules (Scothorne, 1964). Differentiation of cellular organelles are manifest later in fetal life (Altenahr and Wohler, 1971). That fetal thyroid tissue can secrete CT early in gestation is suggested by the better growth of fetal chick bones in the presence of 8-day fetal chick thyroid tissue than in its absence (Gaillard and Thesingh, 1968). There is increased fetal CT secretion in rats toward the end of gestation (Garel, 1970; Feinblatt and Raisz, 1971). Calcium infusion in the fetus has suppressed the hypocalcemic effect of CT (Garel, 1970). It has been suggested that this effect might be mediated by inhibition of bone resorption, as in the adult. Exposure of fetal rat thyroid tissue *in vitro* to increasing concentrations of calcium (to 2½ times normal levels) increased the release of CT; it inhibited PTH-stimulated calcium release from fetal bone threefold (Feinblatt and Raisz, 1971). When both calcium and magnesium concentrations were physiologic (Ca/Mg = 1.0/0.8 mM) additional CT caused some inhibition of PTH-stimulated release of ^{45}Ca from fetal bone. When the magnesium concentration was reduced to 0.4 mM or raised to 1.6 mM, a slight increase in CT secretion resulted, which increased the percentage inhibition of release of calcium slightly. When magnesium was further raised to 3.2 mM, the CT-induced percentage inhibition of calcium release rose a little more, although none of the changes were sufficient to be considered significant. There has been considerable experimental evidence that CT increases bone calcification and new bone formation directly (Matthews *et al.*, 1972; Wase *et al.*, 1967; Pallasch, 1968; Ziegler and Delling, 1969; Delling *et al.*, 1970; Gaillard and Thesingh, 1968; Salomon *et al.*, 1973), independent of its counteraction of demineralization. Thus, the lowering of plasma levels of calcium, magnesium, and phosphorus in response to CT (Garel *et al.*, 1968, 1969; Garel and Barlet, 1974) might indicate utilization of those elements in bone formation. The high CT levels in the fetus are likely to take part in bone growth and calcification (Samaan *et al.*, 1973b).

12.3.1.2. Interrelationships with Gestational Hypervitaminosis D

Magnesium deficiency has been implicated in placental and fetal abnormalities. Placental calcification has been reported in magnesium-deficient rats (Dancis *et al.*, 1971). Since most rat diets are rich in calcium, phosphorus, and vitamin D, further work is necessary to determine how much of the placental damage in that study might have been caused by the other nutrients. Hypervitaminosis D during pregnancy has been implicated in human and experimental placental damage. In rats, it has also caused fetal bone damage (Ornoy *et al.*, 1969). That gestational hypervitaminosis D (which increases magnesium loss) causes both placental and fetal bone damage is provocative, but does not separate the possible direct effect of vitamin D toxicity from the presumed effect of magnesium deficiency on the placenta. That

magnesium deficiency causes bone damage has been clearly demonstrated after birth. Vitamin D excess, given to pregnant rabbits, has caused premature closure of the fontanels, osteosclerosis, and palatal abnormalities (Friedman and Mills, 1969). Nonetheless, the levels of the 25-OH-D_3 metabolite of young of rabbits given toxic doses of vitamin D have been subnormal (Mehlhorn *et al.*, 1977), suggesting abnormality in vitamin D metabolism under these conditions.

Detailed study of the fetal bone abnormalities caused by toxic dosage of vitamin D in pregnant rats (40,000 units D_2) showed that the fetuses had 61% decreased bone ash by the 21st day of gestation, shortened thin diaphyses, and abnormal epiphyseal cartilage. Pups of rats given half as much vitamin D (Ornoy *et al.*, 1972) had bone deformities consisting of kyphoscoliosis and distortions of the long bones. There was less osteoid in the metaphyses, there were many metaphyseal fractures, and diaphyseal bone was short, distorted, and with much thinner than normal periosteal bone. By the 30th postnatal day, some of the pups had epiphyseal fractures. The authors observed that the prenatal vitamin D excess resulted in lasting defects in bone formation and imperfect healing of fractures in the newborn, that resembles some of the characteristics of osteogenesis imperfecta. When prenatal vitamin D excess causes osteopenia, it is possible that magnesium deficiency might complicate the picture, in that it might militate against CT release, high intakes of magnesium (like hypercalcemia) stimulating CT secretion. It should be kept in mind that fetal magnesium stores are likely to be suboptimal in magnesium-deficient mothers. Experimental magnesium deficiency has caused bone lesions *(supra vide)*. Epiphyseal separation and osteochondrosis have been reported in premature infants (Griscom *et al.*, 1971) and have been reported in older children with magnesium deficiency (Miller, 1944; Klingberg, 1970) or with the bone lesions of celiac disease of children (Parsons, 1927) or adults (Bronsky, 1970; Prost *et al.*, 1972), which has been associated with either magnesium or vitamin D deficiency or both (Prost *et al.*, 1972). It has also been associated with "pseudohypoparathyroidism" with parathyroid hyperplasia and hyper- rather than hypoparathyroidism, and is resistant to the action of PTH, further suggesting magnesium depletion.

12.3.2. Magnesium Deficiency and Bone Disease in Low-Birth-Weight Infants

Low-birth-weight infants, who might reflect intrauterine malnutrition rather than prematurity, are especially prone to magnesium depletion. The pathogenesis of the lesions described in this section is difficult to understand and interpret, conflicting findings having been reported and many factors interrelating. For example, magnesium depletion can cause decreased release of PTH and decreased target organ responsiveness (Fig. 12-1.). Yet acute magnesium deficiency has increased PTH release and chronic suboptimal magnesium intake has caused parathyroid hyperplasia (Larvor *et al.*, 1964a). Vitamin D excess causes hypercalcemia, which can increase CT secretion and cause osteosclerosis (Fig. 12-2) or can cause magnesium loss and osteopenia (Fig. 12-1). Magnesium deficiency in infancy can cause hypocalcemic tetany and can be involved in vitamin D refractoriness. Both magnesium and vitamin D deficiency can cause fetal, neonatal, and later osteopenias.

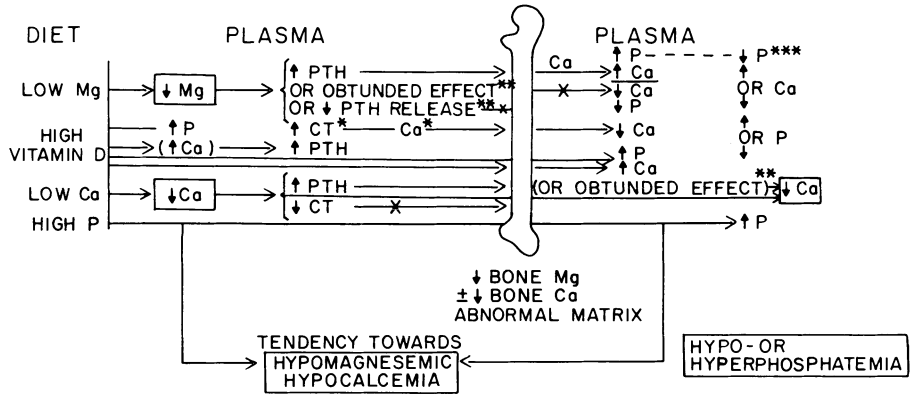

FIGURE 12-1. Low dietary magnesium and calcium and high vitamin D + phosphorus: hypomagnesemia, hypocalcemia, and osteopenia. *Acute magnesium deficiency; **severe magnesium deficiency; ***PTH renal effect.

Yet mothers with presumptive magnesium deficiency and placental pathology have given birth to infants who developed osteosclerosis almost indistinguishable from that of rodents with hypervitaminosis D. Conversely, mothers with intestinal malabsorption, which probably interfered with absorption of both magnesium and vitamin D, gave birth to infants with congenital rickets. Furthermore, low-birth-weight infants have been shown to require vitamin D supplementation, above that in their fortified formula to avoid rickets (Lewin *et al.*, 1971). It should be recalled, here, that magnesium deficiency increases vitamin D requirements. Vitamin D supple-

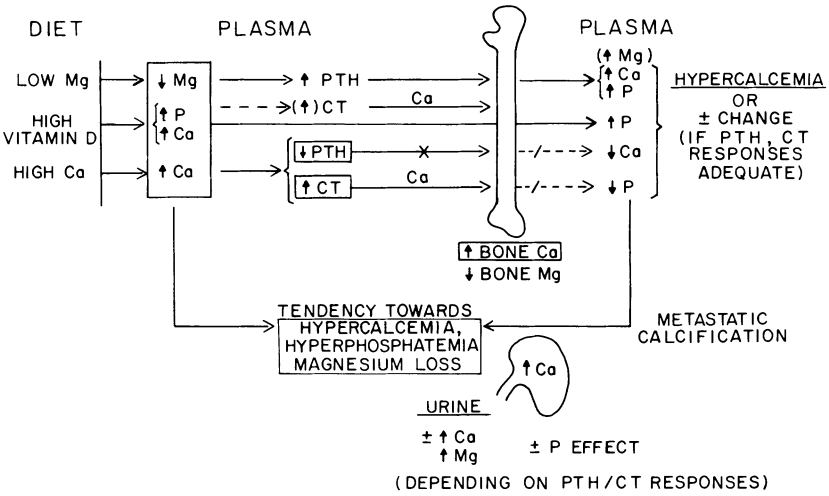

FIGURE 12-2. Low dietary magnesium and high calcium and vitamin D: hypercalcemia, magnesium loss, and osteosclerosis.

ments have increased, significantly, plasma 25-OH-D_3 levels in maternal, cord, and neonatal blood (Belton *et al.*, 1975, 1977). The possibility of abnormal vitamin D utilization with gestational excess (Mehlhorn *et al.*, 1977) should be kept in mind, low levels having been seen.

Experimental evidence has been presented that suboptimal supply of magnesium to the fetus can stimulate fetal PTH secretion. Whether it can contribute to abnormal vitamin D metabolism in the mother or the fetus should be explored. The degree to which maternal and fetal bone stores are utilized (under the influence of PTH secretion and vitamin D administration) probably depends upon the ratio of PTH and calcitonin (CT) levels and the metabolism of vitamin D, which are affected by both calcium and magnesium levels. Although fetal osteosclerosis has been correlated with excessive vitamin D, calcium, and phosphate administration, magnesium-deficient fetuses are also at risk of bone loss or defective formation.

Indirect evidence that this can be so derives from the osteoporosis, epiphyseal separation, poorly mineralized subperiosteal new bone, enlargement of costochondral junctions, metaphyseal cupping, and spontaneous fractures in three premature infants of women with placental pathology. Two of the mothers were preeclamptic and one was a young multipara who had two previous premature deliveries (Griscom *et al.*, 1971): All of the women were probably magnesium deficient, two as a result of bearing twins and having preeclampsia, and one because of frequent pregnancies at a young age. That the infants might also have been magnesium deficient is suggested by the fact that two were survivors of twin pregnancies and one was premature. The twins who did not survive had been stillborn in one instance and had died at 10 hours in the other, the latter with thymic involution (such as is seen in infants with long-standing intrauterine distress) and with microfocal myocardial necrosis. The bone disease of these three infants was diagnosed a week before death: a few days after sudden cardiac arrest at 71 days in one, and two months after a cardiac murmur was diagnosed at one month in another. Additional suggestive evidence that magnesium deficiency might have been present was the severe anemia that developed in all three, such as has been produced in the young by experimental magnesium deficiency in pregnant rats (Cohlan *et al.*, 1970) and in nonpregnant rats (Elin *et al.*, 1971b; Elin, 1973, 1976/1980).

Griscom *et al.* (1971) pointed out that demineralization of bone may not be rare in low-birth-weight infants in the early weeks or months of life. The first such case, an atrophic newborn infant with osteogenesis imperfecta in association with arteriosclerosis, was reported by Johansson (1921–1922). Dystrophic osteomalacia of prematurity has been reported from France (Boissiere *et al.*, 1964), and is characterized by icterus and penumonitis as well as by bone disease. Griscom *et al.* (1971) found many similarities in the three infants they reported to those of the French infants (Boissiere *et al.*, 1964). The disorder usually does not become manifest until the third month of life and commonly appears in twins. Fractures, subperiosteal new bone, and osteoporosis characterize the disease. However, only one of the three American infants of Griscom *et. al* had icterus, and that to only a slight degree. It was seen in 22 of 26 of the French infants. The American infants also did not present with hypocalcemic tetany, such as was reported from France. Griscom *et al.* (1971) considered the picture to reflect a metabolic, probably nutritional dis-

order other than rickets, and considered it likely to be fairly common among premature infants.

Another premature infant that developed rarefaction of ribs and scapula and spontaneous rib fractures by the third month of life, and also had anemia considered typical of prematurity, was diagnosed as rachitic (Keipert, 1970). This infant was the fourth child born in a difficult labor to an apparently normal mother. Intermittent apneic attacks began at 11 days. Despite vitamin D supplementation of 1,400–800 IU/d, some evidence of rickets persisted at nine months of age. The author commented that fractures are more common in rachitic than in normal bones, but observed that nonrachitic premature bones are also easily traumatized. He noted that the subperiosteal proliferation of prematurity is not related to vitamin D deficiency, and that Eek *et al.* (1975) found such changes earlier in premature infants fed cows' milk than in breast-fed prematures. Eek *et al.* (1957) postulated that double periosteal contours appeared in such infants when deposition of minerals increased after a period of poor mineralization. Tsang *et al.* (1977) have reviewed data on the abnormal and delayed skeletal mineralization in very low-birth-weight infants. Their group has shown that extrauterine bone mineralization lags significantly in such infants (Minten *et al.*, 1976; Steichen *et al.*, 1976).

It is provocative that the low-birth-weight infants who develop bone lesion rarely exhibit symptomatic hypocalcemia, such as is seen in those free of osteopenia. Possibly fetal hyperparathyroidism had mobilized fetal bone calcium. However, an alternative possibility must also be considered, that of the response of maternal, fetal, and neonatal C cells to changes in calcium and magnesium levels. High CT levels might contribute to both low plasma levels of calcium and magnesium, increasing bone mineralization.

12.4. Magnesium Status and Vitamin D Requirements and Responses

12.4.1. Increased Vitamin D Requirements of Magnesium Deficiency

The first clue to the vitamin-D-sparing effect of magnesium administration was provided by Huffman *et al.* (1930), who found that a rachitic calf recovered when magnesium carbonate was added to his diet, which was low in calcium but adequate in phosphorus. When it was withdrawn, the abnormal signs recurred. His ribs were soft and broke easily. Calves fed whole milk for 45 days, after which they were given only skim milk and grain [a rachitogenic ration, with a high phosphorus/calcium ratio (Huffman *et al.*, 1930, 1935)], developed hypocalcemia and hyperphosphatemia by 95 days. Magnesium carbonate administration, alone, did not cure the rickets, but when it was given with suboptimal amounts of vitamin D, the biochemical and clinical signs of rickets were corrected. The ash and mineral content of the bones indicated better utilization of calcium and phosphorus when magnesium supplements were given. R. H. Smith (1957, 1961) observed that magnesium supple-

mentation of milk-fed calves that had developed hypocalcemia restored normal serum calcium levels even without vitamin D supplementation and speculated that magnesium might exert its effect on bone/extracellular equilibrium (of calcium). Magnesium-deficient calves had hypocalcemia requiring 70,000 IU/day to correct (R. H. Smith, 1958).

Baby pigs developed rickets on a normally balanced calcium and phosphorus intake (0.8% and 0.6% of the diet, respectively, when they were given less than 100 IU of vitamin D/kg of diet (E. R. Miller *et al.*, 1964b). Most exhibited a moderate fall in plasma magnesium, even on what was shown to be optimal magnesium intakes: 350 ppm of diet (E. R. Miller *et al.*, 1965a), particularly in those that developed tetany. All developed hypophosphatemia and hypocalcemia. Balance studies showed that the vitamin-D-deficient pigs absorbed magnesium, calcium, and phosphorus poorly (E. R. Miller *et al.*, 1965b). Doubling the magnesium intake of pigs given no vitamin D improved their weight gain, and prevented the mortality (that resulted in deaths of three of the four vitamin-D-deficient pigs on the standard magnesium intake) but neither prevented their rickets nor corrected their hypocalcemia or hypophosphatemia (E. R. Miller *et al.*, 1964b). Thus, like most human infants, baby pigs require exogenous vitamin D to prevent rickets. Increasing the magnesium intake exerts a partially sparing effect on vitamin D requirements but cannot replace it.

On the other hand, when vitamin D supplements 18-fold higher than the antirachitic amount are given to baby pigs, the greatest strength and elasticity of the femur is obtained with an optimal magnesium intake of 325 ppm (E. R. Miller *et al.*, 1965b). Analysis of rib ash showed no significant effect of low dietary magnesium on percentage of calcium or phosphorus, but a significant reduction in percentage of magnesium. Pigs on low-magnesium intakes, however, exhibited significantly less breaking strength and elasticity (Fig. 12-3). Since the elasticity of the bone is a function of the amount of matrix, the drop in elasticity—but not in bone ash, calcium, and phosphorus of the magnesium-deficient vitamin-D-loaded pigs—reflects the drop in bone magnesium, which is necessary for normal bone matrix formation.

Rats, which are the most commonly employed laboratory animals and with whom most vitamin D and magnesium interrelationships have been studied, differ markedly from the ruminants, pigs, and people as regards their susceptibility to rickets and their response to magnesium deficiency. They do not develop rickets, even when given no vitamin D supplementation, unless they are given diets high in calcium and low in phosphorus (Steenbock diet, cited by Shelling and Asher, 1932). McHargue and Roy (1930) showed that rats fed a normal diet, not supplemented with vitamin D and not exposed to ultraviolet light, remain free of rickets. Au and Raisz (1965) confirmed that rats not supplemented with vitamin D do not develop rickets unless their diets have a high ratio of calcium to phosphorus (0.8% Ca/0.1% P). Rats on high phosphorus to calcium ratios (0.1% P/0.03% Ca) had decreased bone density, but not rickets. The effect of high (14,500 ppm) and normal (6,500 ppm) intakes of calcium fed to groups of rats fed a normal amount of phosphorus (6,100 ppm), but low in magnesium (30 ppm), was studied by Rayssiguier and Larvor (1974a). By the tenth day of the low magnesium intake, all of the rats had hypomagnesemia and low levels of magnesium in their bones. Those that had been

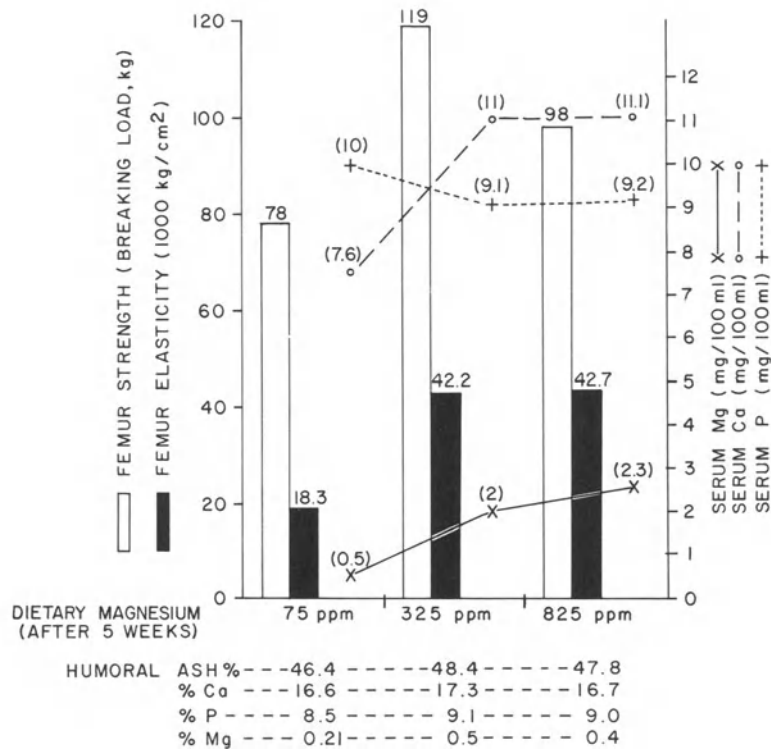

FIGURE 12-3. Serum and bone Mg, Ca, and P in baby pigs on vitamin D 18-fold higher than optimum, normal Ca/P ratio, and low, optimal, and high Mg intakes. (Derived from ER Miller *et al.*, 1965a.)

given high calcium diets the longest (17, versus 10 days), had the lowest bone magnesium levels. Since high calcium intakes interfere with intestinal absorption of magnesium and increase its urinary output (Reviews: Heaton, 1971; Larvor and Durlach, 1971b; Seelig, 1971), the rats made susceptible to rickets might have been magnesium deficient. Furthermore, vitamin D is necessary for optimal intestinal absorption of magnesium in rats (Meintzer and Steenbock, 1955), as well as in pigs *(supra vide)* and other species (Schachter and Rosen, 1959; Worker and Migicovsky, 1961) including man. Despite the defective magnesium absorption of vitamin D deficiency, the early rat studies showed high magnesium/calcium ratios in rachitic bones (possibly a reflection of the high osteoid/mineral ratio of such bones). McHargue and Roy (1930), who cited the early studies (Malcolm, 1904; Mellanby, 1926), found that exposure of rats to ultraviolet light for only three to five minutes daily or every other day resulted in better weight gain (than of nonirradiated littermates), but in significantly lower bone and total carcass magnesium levels. This work was done before it was realized that magnesium is an essential mineral, and the authors speculated that the beneficial effects of ultraviolet ratio might be the result of eliminating excess magnesium.

Supplementation with vitamin D of rats made rachitic by low phosphorus diets

corrects the hypophosphatemia and heals the rickets (Tanaka and DeLuca, 1974), an effect attributed to a vitamin-D-dependent phosphate transport mechanism (DeLuca, 1976). In 1941, Harrison and Harrison showed that vitamin D increases renal tubular reabsorption of phosphate. Possibly vitamin D's increase of the intestinal absorption of magnesium might also play a role, magnesium deficiency having been shown to exert a phosphaturic effect, even in parathyroidectomized rats (Ginn and Shanbour, 1967). VonEuler and Rydbom (1931) noted the antirachitic effect of adding magnesium to a rachitic diet fed to rats and considered this effect possibly due to magnesium-induced increase in serum phosphatase activity.

In contrast, magnesium deficiency decreases responsiveness to vitamin D in ruminants and rats (R. H. Smith, 1961; Larvor *et al.*, 1964b; Lifshitz *et al.*, 1967a,b). Magnesium-deficient calves required 70,000 IU/day of vitamin D to attain normocalcemia; physiologic doses of vitamin D were not effective (R. H. Smith, 1958). Similarly, Lifshitz *et al.* (1967b) found that magnesium-deficient rats did not develop a calcemic response to 100 IU of vitamin D a week, but did when the vitamin D dosage was increased 10-fold. Their studies suggested that the poor response of serum calcium in magnesium-deficient rats, to physiologic doses of vitamin D, was due to decreased mobilization of calcium from the skeleton.

Whether impaired mineral mobilization in association with high calcium and vitamin D intake might account for the osteosclerosis seen in rats given intermittent high doses of vitamin D (Storey, 1960), and is mediated by magnesium-deficiency-induced abnormal bone development, deserves study. Storey (1960) observed that large daily doses of vitamin D inhibited endochondrial growth in rats, caused bone resorption and, later uncalcified matrix (osteoid), such as is seen in rickets. When the vitamin D was given intermittently, dense metaphyseal bone was formed in striations, which contained abnormal cartilage, changes resembling those seen in osteopetrosis. It is noteworthy, thus, that comparable changes were seen in infants and children with infantile hypercalcemia, commonly with the supravalvular aortic stenosis syndrome of clinical vitamin D overdosage. Since vitamin D excess causes magnesium loss, it is not surprising that its use (i.e., in milk, which also delivers ample calcium and phosphate) can produce changes in the matrix, such as is seen in magnesium deficiency as well as bone hypermineralization.

Lifshitz *et al.* (1967b) noted the lag between the time a physiologic dose of vitamin D was given and the calcemic response, and suggested that magnesium's mediating effect might be in its transformation to another form. Since then, it has been demonstrated that vitamin D is hydroxylated to active steroid hormones (e.g., in liver and kidney), and that some of the enzymatic steps require magnesium (Norman, 1968, 1971; DeLuca, 1969; Horsting and DeLuca, 1969; Norman *et al.*, 1975/1977). Its deficiency in rats has interfered with the activity of the $1,25\text{-}(OH)_2D_3$ on calcium mobilization from bone, but has not prevented its enhancement of intestinal calcium absorption (Rayssiguier *et al.*, 1974b, 1975).

The cited experimental evidence that magnesium deficiency causes relative refractoriness to vitamin D, very high doses being required for a calcemic response, and that magnesium repletion restores the responsiveness to physiologic doses *(supra vide)*, is reflected by the refractoriness of hypomagnesemic patients to vitamin D. It suggests that the occasional report of correction of vitamin-D-refractory

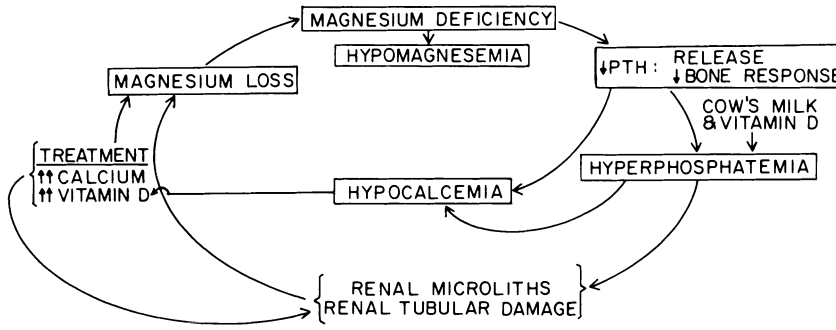

FIGURE 12-4. Vicious cycle: Correction of infantile hypocalcemia by calcium + vitamin D (without magnesium).

rickets by magnesium might be indicative of the need to evaluate all patients with vitamin-D-unresponsive bone disease for their magnesium status. Conversely, Durlach (1969, 1971) pointed out that patients with latent tetany of magnesium deficiency require less vitamin D when their magnesium deficit is repaired and must have their serum calcium monitored to avoid damage caused by hypercalcemia.

The magnesium/vitamin D/calcium/phosphorus interrelationships are particularly complex. Focusing only on magnesium is unrealistic. Disregarding magnesium is equally unrealistic. Considering only the magnesium/vitamin D interrelationships, if there is a deficiency of magnesium in infancy, for example, there is likely to be impaired response to vitamin D (and to PTH) with resultant hypocalcemia. However, we cannot ignore the hyperphosphatemia of infancy, which is contributed to by the cows' milk and the hypoparathyroidism, and which is enhanced by vitamin D therapy of the hypocalcemia. Thus, in attempting to correct infantile hypocalcemia by calcium loads and calcemic agents a vicious cycle can be established that causes direct loss of magnesium and might damage the area of the renal tubules where magnesium is actively reabsorbed (Fig. 12-4).

12.4.2. Vitamin-D-Refractory Rickets and Osteomalacia

12.4.2.1. Hypophosphatemic Hyperparathyroid Rickets

Hypophosphatemic (vitamin-D-dependent or vitamin-D-refractory) rickets is now the most common cause of rickets in children, and the pathogenesis is still obscure (Cohanim *et al.*, 1972; Brickman *et al.*, 1973). The syndrome was first attributed to hyperparathyroidism secondary to malabsorption of calcium (Albright *et al.*, 1937), and then to an often familial intrinsic renal tubular defect of phosphate reabsorption (B. Robertson *et al.*, 1942; Dent, 1962; Fanconi, 1955; Frame and Smith, 1958; Barbour *et al.*, 1966). Despite the hypophosphatemia, biopsy of the epiphyseal area showed normal content of phosphate (Kuhlman and Stamp, 1964) and also above normal levels of bone alkaline phosphatase, hypertrophic cartilage

cells, and thick areas of uncalcified osteoid. Subsequent work has confirmed both hyperparathyroidism (Lafferty *et al.*, 1962; Riggs *et al.*, 1969), usually secondary to intestinal malabsorption (Blackard *et al.*, 1962; Falls *et al.*, 1968; Reitz and Weinstein, 1973), and a genetic X-linked defect in renal tubular reabsorption of phosphate (Glorieux and Scriver, 1972; Glorieux *et al.*, 1973; Scriver, 1973). T. F. Williams (1968) commented on the apparently simple genetics but multiorgan sites of expression in familial hypophosphatemic vitamin-D-resistant rickets. He called for a unifying way to explain the: (1) decreased renal tubular reabsorption of phosphate, (2) decreased intestinal reabsorption of calcium, (3) bony abnormalities, including both osteomalacia and overgrowth, and (4) improvement of calcium absorption and rickets, but not the phosphaturia, with large doses of vitamin D.

Possibly a form of the genetic defect, isolated magnesium malabsorption, is contributory, and might even be a common denominator. This is a point requiring intensive study, and not by measurement of serum magnesium levels. Analysis of bone biopsies for phosphatase and magnesium levels, and metabolic balance studies to ascertain the percentage absorption of orally administered magnesium might be useful. Since such patients are commonly loaded with calcemic agents and phosphates in the attempt to correct their hypocalcemia and hypophosphatemia, and such treatment has increased renal calcinosis, determination of percentage renal retention of magnesium might not be a good index of magnesium depletion. Renal magnesium wasting might result from formation of renal tubular microliths, with damage to the ascending limb of the loop of Henle, where active tubular reabsorption of magnesium takes place. This would perpetuate a magnesium deficit caused by intestinal malabsorption of magnesium.

Magnesium deficiency might be involved in several facets of vitamin D resistance. Both hyperparathyroidism and hypomagnesemia have been implicated in hypophosphatemia (Review: Knochel, 1977), and since familial hypophosphatemia has been found in vitamin-D-resistant rickets in infants and adults (Stickler, 1969; Arnaud *et al.*, 1970; Morgan *et al.*, 1974), there might be a common denominator. There have been several studies that demonstrate abnormal magnesium metabolism and levels, and a few that have shown clinical and biochemical improvement with magnesium therapy.

McCance (1946) reported negative magnesium, calcium, and phosphorus balance in a girl whose vitamin D resistance, osteomalacia, and pseudofractures developed during adolescence. Rosen and Finberg (1972, 1973) found strongly negative magnesium balances in children with active vitamin-D-dependent rickets, which became strongly positive when they had been healed as a result of administration of 25(OH)D_3, an active vitamin D metabolite. However, despite negative magnesium balances during the active phase of the disease, serum magnesium levels were within normal limits. Among the conditions found to be associated with low total and ultrafiltrable magnesium levels, reported by Prasad *et al.* (1961), was a patient with vitamin-D-resistant rickets before treatment.

Administration of magnesium to two children who had rickets, hypocalcemia, and high levels of alkaline phosphatase, despite very high doses of vitamin D_2, corrected the biochemical abnormalities and produced X-ray evidence of bone heal-

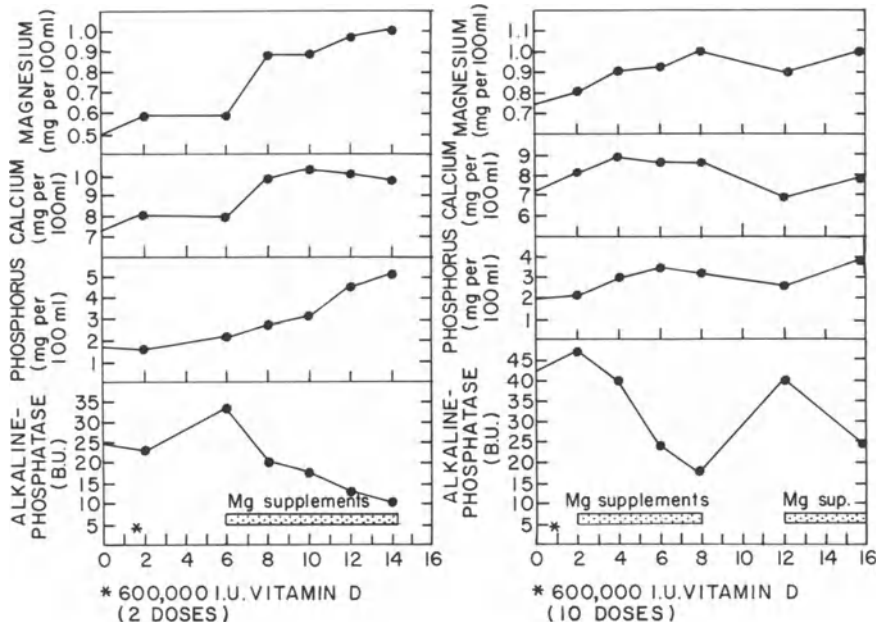

FIGURE 12-5. Responses of vitamin-D-resistant rickets to magnesium. (Derived from Reddy and Sivakumar, 1974.)

ing (V. Reddy and Sivakumar, 1974). These investigators reported a 5-year-old boy and a 2-year-old girl with rickets, whose hypocalcemia and serum alkaline phosphatase levels of 24.1 and 42.6 Bodansky units failed to respond to several doses of 600,000 IU of vitamin D_2. In the boy, serum alkaline phosphatase levels rose further following the high-dosage vitamin D therapy. Severe hypomagnesemia (0.4 mEq/liter) was then detected and oral magnesium supplementation (10 mEq/day as $MgCl_2$) was started. All biochemical determinants became normal within 4 weeks. The serum magnesium level of the baby girl, who had received 4,000 IU of vitamin D from early infancy, was found to be 0.6 mEq/liter on admission. She was given 600,000 IU of vitamin D daily for 10 days without biochemical improvement. Magnesium supplementation resulted in prompt fall of high levels of serum phosphatase activity, and rises in serum magnesium, calcium, and phosphorus. She was not given the prescribed magnesium at home, and within a month her biochemical abnormalities had recurred. They were promptly corrected on reinstitution of magnesium therapy (Fig. 12-5). Since the diets of these children were not deficient in magnesium, the investigators believe they are probably magnesium malabsorbers.

Rapado *et al.* (1975) termed the rickets of their 12-year-old patient "magnesium-deficient rickets." She had a long history of polyuria and was found to have nephrocalcinosis with persistent hypercalciuria. After 7 months of treatment with sodium cellulose phosphate (10g/d), her hypercalciuria was corrected, but she developed hypocalcemia, and increased serum alkaline phosphatase. Treatment

was then changed to hydrochlorothiazide for two months, after which she developed tetany and osseous pain. Her serum calcium was then 6.9 mg/100 ml, her serum magnesium was 0.5 mEq/liter and her urinary outputs of magnesium and calcium were subnormal. She exhibited subnormal response to PTH. By this time she had signs of overt rickets in wrists and knees. Intramuscular magnesium supplementation (1.5 g/day) for a month resulted in disappearance of the radiologic signs of rickets and correction of the hypomagnesemia and hypocalcemia. On readmission six weeks later, her serum magnesium was again low (1 mEq/liter). On a normal magnesium intake (336 mg/day) she absorbed only 0.2%; thus she represented another instance of magnesium malabsorption. Rapado and Castrillo (1976/1980a) have identified another patient with magnesium-dependent rickets, nephrocalcinosis, and who has magnesium malabsorption. Rapado *et al.* (1975) recommend that patients with vitamin-D-resistant rickets, nephrocalcinosis, or failure in response to PTH be evaluated for magnesium deficiency.

Patients with steatorrhea, enteritis, or bypass surgery for obesity have exhibited vitamin-D-refractory osteomalacia (Blackard *et al.*, 1962; Prost *et al.*, 1972; Reitz and Weinstein, 1973; Medalle *et al.*, 1976). Although hypocalcemia is more frequently reported in this disorder, and the hypophosphatemia is commonly attributed to resultant secondary hyperparathyroidism, magnesium deficiency is also common. Reversal of vitamin D resistance has been produced in such patients with magnesium repletion (Medalle *et al.*, 1976).

Although the magnesium status has been shown to influence the response to vitamin D in animals (magnesium deficiency increasing vitamin D requirements) and magnesium is a cofactor in vitamin D conversion to its active steroid-metabolites, its role in vitamin D metabolism in clinical magnesium depletion is not clear. For example, patients who were hypomagnesemic as a result of malabsorption synthesized no less 1,25-$(OH)_2D_3$ than did normomagnesemic, hypocalcemic, vitamin-D-deficient patients (Lukert, 1976/1980). The active vitamin-D-derived hormones are necessary both for normal intestinal absorption of calcium and for bone calcium turnover (Reviews: Norman, 1974, 1977; DeLuca, 1976). The evidence that vitamin D is necessary for intestinal absorption of magnesium and lowers bone magnesium levels suggests that the active metabolites must also influence magnesium metabolism, and abnormality in vitamin D metabolism probably influences bone integrity as a function, not only of changes in handling of calcium but of magnesium. Avioli *et al.* (1967) found increased levels of vitamin D metabolites without calcium absorptive activity in hypophosphatemic rickets. How such metabolites influence magnesium absorption or bone levels has not been reported.

Vitamin D increases renal tubular reabsorption of phosphorus (Harrison and Harrison, 1941). A vitamin-D-dependent intestinal phosphate-transport mechanism (DeLuca, 1976) can partially explain the hypophosphatemia of vitamin-D-refractory rickets. Association of abnormal vitamin D metabolism with secondary hyperparathyroidism (Arnaud *et al.*, 1970) supports the premise that hyperparathyroidism, whether secondary to intestinal malabsorption or to abnormal vitamin D metabolism, contributes to impaired phosphate reabsorption by the kidneys. Clinical evidence of the importance of the abnormality of vitamin D metabolism in hypophos-

phatemic rickets has been obtained by demonstration of response of patients with this disorder to the 25-(OH)D_3 (Rosen and Finberg, 1972, 1973), to the 1,25$(OH)_2D_3$ (Fraser *et al.*, 1973; Avioli and Haddad, 1973; Balsan *et al.*, 1975) and to 1,α(OH)D_3 (Balsan *et al.*, 1975; Rosen and Finberg, 1975/1977). The active metabolites, like the parent substance, vitamin D_3, correct the malabsorption of calcium and the impaired bone mineralization, but do not influence the form of the disease that is characterized by intrinsic defective renal tubular phosphate reabsorption (Brickman *et al.*, 1973; Glorieux *et al.*, 1973). Possibly relevant to this partial failure of treatment is the demonstration of phosphaturia in magnesium-deficient rats (despite their hypercalcemia, and even in those that were parathyroidectomized) by Ginn and Shanbour (1967).

12.4.2.2. Hyperphosphatemic, Hypoparathyroid Osteopenia

A paradoxical facet to vitamin D resistance is that, in addition to its association with hyperparathyroidism and hypophosphatemia, magnesium-reversible vitamin D refractoriness has long been recognized in hypoparathyroidism with hyperphosphatemia (Homer, 1961; K. Jones and Fourman, 1966; Harrison *et al.*, 1967). A child with idiopathic hypoparathyroidism who had hypocalcemia and low serum alkaline phosphatase levels responded to PTH with phosphaturia, but without correction of her hypocalcemia (Rösler and Rabinowitz, 1973). She was then given up to 600,000 IU of vitamin D and 3–4 g of calcium lactate for 13 weeks, and then dihydrotachysterol, without raising her blood calcium level. Her serum magnesium was then found to be 0.5 mEq/liter, and she developed convulsions and tetany. Magnesium repletion produced rapid improvement. Medalle and Waterhouse (1973) reported a biochemical picture of hypoparathyroidism, hypocalcemia and hyperphosphatemia in a patient with severe magnesium depletion of chronic alcoholism, and suggested that magnesium deficiency be considered in the differential diagnosis of hypoparathyroidism, pseudohypoparathyroidism, and renal failure. Their patient did not exhibit a normal phosphaturic response to PTH while she was magnesium depleted. Magnesium therapy corrected her hyperphosphatemia promptly; correction of her hypocalcemia was more gradual. This finding suggested to the investigators that hyperphosphatemia does not occur unless the magnesium depletion is severe. They noted that it occurs less frequently than does hypocalcemia in magnesium-deficient patients, and has been reported with selective experimental magnesium deficiency (Shils, 1969a) or with isolated magnesium malabsorption (Dooling and Stern, 1967; Skyberg *et al.*, 1967; 1968; Stromme *et al.*, 1969; Nordio *et al.*, 1971).

It might be well, also, to ascertain whether the high vitamin D requirements of low-birth-weight infants (who are also subject to hypoparathyroidism and hyperphosphatemia) might be contributed to by magnesium inadequacy. Vitamin-D-resistant rickets of biliary atresia, which is responsive to 25-OHD_3 (Daum *et al.*, 1976; Rosen and Finberg, 1975/1977), might also be responsive to magnesium, magnesium deficiency having been demonstrated in such infants (A. Kobayashi *et al.*, 1967, 1974). On the other hand, a defect in intestinal absorption of magnesium , as well as of calcium, has been found in idiopathic hypoparathyroidism, which improved following treatment with 25-OH D_3 (Rosen and Finberg, 1975/1977).

12.4.3. Other Abnormal Function of, or Response to, Parathyroids

Magnesium deficiency affects parathyroid hormone (PTH) secretion, and target organ response, and several syndromes are associated primarily with skeletal abnormalities that might have abnormal magnesium matabolism as a common denominator. For example, idiopathic hypoparathyroidism and pseudohypoparathyroidism and variations of these disorders that have been given cumbersome names (e.g., pseudopseudohypoparathyroidism, pseudohypohyperparathyroidism) might be explicable on the basis of different phases and degrees of magnesium deficiency and its influence on response to calcemic or hypocalcemic therapy. Bronsky (1970) criticized the nomenclature used for the variations in disorders that are associated with Albright's osteodystrophy (brachydactyly, stocky body, and round face) or dyschondroplasia with soft tissue calcinosis. Selected from his tabulated forms of parathyroid disease are several that might derive from abnormalities of magnesium metabolism, or from maternal, perinatal, or later dietary imbalances (Table 12-1). Patients with osseous or soft tissue calcinosis frequently have close relatives with parathyroid disease or convulsive disorders, which is suggestive of a possible contributory magnesium deficit. Bronsky (1970) stressed the relationship of steatorrhea to parathyroid disease (both hypersecretion and resistant hypoparathyroidism), an observation that supports the concept of underlying magnesium deficiency. Discussed earlier are gestational hyperparathyroidism and neonatal hypoparathyroidism and their likely interrelationships with magnesium deficiency.

Albright *et al.* (1942), who first described the pseudohypoparathyroid dyschondroplasia syndrome, noted that patients with this disorder had convulsions themselves and had siblings with epilepsy, were mentally retarded, and were resistant to high doses of calcemic agents. These manifestations, and the histories of infantile respiratory distress (reported in the original and subsequent cases) resemble those of infants who developed cardiovascular and/or renal abnormalities that are speculated also to be related to magnesium deficiency. The patient reported by C. Lowe *et al.* (1950), who had an early symptom-complex very much like infants with

TABLE 12-1. Parathyroid Diseases Possibly Caused by Magnesium Deficiency

"Idiopathic" hypoparathyroidism
Neonatal
Familial
Hypoparathyroidism secondary to hypercalcemia (of nonparathyroid origin)
Hormonal unresponsiveness to PTH
Familial ± brachydactyly, ± subcutaneous calcinosis
Secondary to malabsorption
Hyperparathyroidism
Familial; idiopathic
Multiple endocrine neoplasias
Secondary to chronic hypocalcemia
Secondary to renal failure
Secondary to malabsorption

hyperreactivity to vitamin D, early developed signs of vitamin-D-resistant rickets and spontaneous fractures, such as are seen in hypophosphatasia (related to magnesium deficiency). When she was found to have steatorrhea, the authors speculated that malabsorption might have contributed to her disorder; the malabsorption certainly could have caused magnesium depletion. Talbot *et al.* (1954) described the syndrome in twins, and commented that hypocalcemic symptoms of this disorder usually date from the neonatal period, further suggestive evidence of magnesium deficiency.

An infant who died at two months of age, who had neonatal hypoparathyroidism, hypocalcemia, and hypomagnesemia, had had similar signs, persistent diarrhea, and renal tubular acidosis, but no X-ray evidence of rickets or soft tissue calcinosis. PTH injection evoked a phosphaturic and calcemic response, but lowered her serum magnesium to subnormal levels. Calcium therapy further lowered it, and caused hypercalcemia (Taitz *et al.,* 1966). At autopsy, neither parathyroid nor thymic tissue was found, and there were intraluminal renal tubular calcium deposits. The bones were not examined. Whether this case reflects profound prenatal parathyroid suppression, or a genetic defect, complicated by a metabolic disorder as proposed by the investigators, and whether longer survival would have resulted in overt skeletal abnormalities, is not possible to aver.

The manifestations of the disorders categorized as "idiopathic" hypoparathyroidism and pseudohypoparathyroidism or dyschondroplasia, predominantly on the basis of presence or absence of phosphaturic response to PTH, were compiled by Bronsky *et al.* (1958). Their tabulation of symptoms and signs of patients diagnosed as "idiopathic" or "pseudohypoparathyroid" (Table 12-2) and their comment that both are idiopathic, the cause not being known, is valuable. It should be noted, however, that current emphasis is on failure of both kidneys and bone of pseudohypoparathyroid patients to respond to PTH, and on failure of 3′,5′ cyclic adenine monophosphate (cAMP) response (Chase *et al.,* 1967, 1969; Drezner *et al.,* 1973). That this abnormality might underlie the refractoriness of bones and kidneys to PTH (Coburn *et al.,* 1972) points toward a possible underlying magnesium deficiency, the synthesis of cAMP having an absolute magnesium requirement (Sutherland *et al.,* 1968).

Evidence has been presented that prenatal magnesium deficiency can contribute to neonatal hypoparathyroidism, and that subsequent dietary imbalances might predispose to permanent damage. Not only the cardiovascular system, but the skeletal and renal systems can be affected, the manifestations depending on combinations of genetic metabolic abnormalities, dietary imbalances, and treatment. Perhaps the higher incidence of thickened calvaria and the much higher incidence of soft tissue calcinosis and mental retardation of the pseudohypoparathyroid group than of the "idiopathic" group might reflect a (postulated) greater magnesium deficit and a consequent need for higher doses of calcemic agents to correct hypocalcemia, with resultant signs resembling those of infantile hypercalcemia. The coarse trabeculation of the short bones of this group of patients, in fact, resembles that seen in experimental magnesium deficiency. Also, the occasional exostosis or tumorlike growth on long bones resembles that seen in patients with hypophosphatasia or osteogenesis imperfecta (speculated to be contributed to by magnesium

TABLE 12-2. Comparison of Manifestations of Idiopathic and Pseudohypoparathyroidism[a]

	Idiopathic hypoparathyroidism (50 cases) (Phosphaturic response to PTH; calcemic response to high-dosage calcemic agents)	Pseudo-hypoparathyroidism (40 cases) (resistance to PTH and to calcemic agents)
A. *Similarities*		
Hypocalcemia	← Rarely above 7.5 mg% in both →	
Hyperphosphatemia	← Rarely above 5.0 mg% in both →	
Tetany	76%	63%
Convulsions	70%	65%
(Familial)	6%	12%
Muscle cramps rigidity, stiffness, twitching	46%	38%
Abnormal EEG	← Similar abnormal patterns in both →	
Abnormal ECG	← Prolonged QT, ST interval, inverted T wave[b] in both →	
Bone, dental defects (demineralization)	8%	10%
Cataracts	48%	35%
B. *Dissimilarities*		
Stridor, laryngospasm	32%	8%
Paresthesias	32%	12%
Blurred optic discs	0	5%
Papilledema	48%	2½%
Strabismus	0	10%
Psychoses, emotional lability	24%	10%
Mental retardation	18%	63%
Bone (increased density)		
(Generalized)	9%	3%
(Localized)	23%	11%
(Skull)	10%	22%
Exostoses	0	11%
Epiphyseal abnormalities	2½%	13½%
Brachytachtyly, with coarse trabeculation	0	69%
Soft tissue calcinosis		
Subcutaneous	2%	58%
Muscles, tendons	4%	0
Brain		
(Basal ganglia)	28%	48%
(Other sites)	8%	12%

[a]Derived from Review of Bronsky *et al.*, 1958.
[b]Occasional report.

deficiency) and seen in experimental magnesium deficiency. Slipped epiphyses, such as have been reported in a few patients with magnesium deficiency and that are in accord with the epiphyseal abnormalities of experimental magnesium deficiency have also been reported in different forms of pseudohypoparathyroidism (Bronsky *et al.*, 1958; Frame *et al.*, 1972). Young patients with the disorder, termed "pseudohypohyperparathyroidism," who had osteosclerosis in the skull, osteitis fibrosa in long and flat bones, and slipped epiphyses, have had serum magnesium

levels reported within normal limits (Frame *et al.*, 1972). The adolescent girl, who had had resistant rickets and subsequent nephrocalcinosis from infancy, and who developed osteitis fibrosa cystica and parathyroid adenomas after years of high-dosage calcemic therapy, had both hypercalcemia and hypermagnesemia on admission to the hospital (W. Thomas and Fry, 1970). The past history of nephrocalcinosis should predispose to renal magnesium wastage, which either did not exist in this patient or was masked by PTH-mobilization of bone minerals preoperatively. More intensive studies of the magnesium status of such patients are necessary to clarify whether cellular magnesium deficit might exist, despite lack of hypomagnesemia. Studies of magnesium metabolism in members of families with either hypo- or hyperparathyroidism that has a genetic component (whether the complete syndrome exists, or only some of the manifestations) might be fruitful.

The condition termed "renal rickets" has long been known to be associated with severe skeletal distortions, acidosis, renal calcinosis, hyperparathyroidism, and mental and growth retardation (Shelling and Remsen, 1935; Price and Davie, 1937). The child reported by Price and Davie (1937) is of particular interest in building up a case for primary magnesium deficiency, since he was the product of the seventh pregnancy, and had been born the year after a miscarriage and the year before two additional miscarriages. As has been discussed, frequent pregnancies are likely to predispose to fetal magnesium deficiency and to spontaneous abortions. This child had generalized osteoporosis and alternate sclerosis and rarefaction of the skull at the age of 14, florid rachitic changes at the extremities, slipped epiphyses, renal damage, deafness, and evidence of mental retardation. At autopsy, it was found that the radiologic diagnosis of slipped femoral epiphysis was incorrect; he actually had collapse of the metaphysis of the neck of the femur, and bone was replaced by a mixture of fibrous tissue and cartilage. All four of his parathyroids were hyperplastic. There were numerous small foci of calcification in his kidneys. These investigators question whether it is necessary to be certain that the renal lesion has preceded the other findings for a diagnosis of renal rickets to be made, as was the case in the similar boy reported by Shelling and Remsen (1935). That boy had hypercholesterolemia, hypertension and arteriosclerosis, and hyperphosphatemia despite parathyroid hyperplasia, elevated PTH levels, and skeletorenal lesions much like those of the child reported by Price and Davie (1937).

In 1927, L. Parsons described five children with fragile bones and rickets secondary to celiac disease. He noted that the skeletal deformities usually do not develop until the age of seven years. One of his patients had blue sclerae, similar to that seen in osteogenesis imperfecta, which gradually became normal in color as the malabsorption improved. Spontaneous pseudofractures were sometimes seen, severe osteoporosis, and persistently fragile bones, even after control of the malabsorption, and despite treatment with cod liver oil. These manifestations are of interest because of their similarity to those of experimental magnesium deficiency and to diseases speculated to be contributed to by magnesium depletion. Prost *et al.* (1972) have described osteomalacia secondary to malabsorption in adults. They correlated osteomalacia and pseudofractures with hypomagnesemia in two instances, and recommended evaluation of the magnesium status with a view to its repair, in an effort to restore vitamin D responsiveness in such patients.

12.4.4. Osteopetrosis or Osteosclerosis and Hyperreactivity to Vitamin D

12.4.4.1. High Vitamin D and Calcium/Low Magnesium

Skeletal changes similar to those seen in magnesium-deficient animals given diets relatively high in calcium and vitamin D, or in hypervitaminosis D studies, are seen in clinical osteopetrosis. Storey (1960) has reviewed the X-ray, histological, and biochemical findings of this disease. Pathognomonic is alternation of radiopaque and radiolucent transverse bands running parallel to the epiphyseal cartilage of the long bones, and to the surface of other bones. Histological studies have shown that the bone is increased in amount, but abnormal. There is some normal bone, islands of densely calcified cartilage near the epiphyses, and areas of osteoid tissue so poorly calcified as to resemble rickets. Microradiographs show areas of high and low bone density, and exaggerated thick radiopaque "cementing" lines on the surface and concentrically around immature Haversian systems. Intense bone resorption is also occasionally seen. These changes are often accompanied by generalized calcinosis of arteries, kidneys, ligaments and tendons, and other soft tissues. Biochemical changes are inconstant, depending on the stage of the disease. Serum calcium levels are usually normal, but hypercalcemia has been reported. Serum phosphorus is often low, with a Ca × P product suggestive of vitamin-D-deficient rickets, or sometimes of vitamin-D-refractory rickets. Storey (1960) confirmed the bone changes of "hypervitaminosis D rickets" in rats, as described by Ham and Lewis (1934), who found flattened, thinned epiphyses, numerous thickened trabeculae, and matrix ranging from normal to poorly calcified, and then possibly "compensatory" excess osteoid. When he gave high doses of vitamin D intermittently to rats (Storey, 1960), the bone changes were very much like those seen in clinical osteopetrosis. The base of the skull became extremely dense and thick. Storey (1960), puzzled over the bone changes caused by excess vitamin D in his own and other studies and considered mediation by hormonal responses, calcium, phosphorus, and "as yet unelucidated systemic disturbances." The similarity of the excess vitamin-D-induced changes of the epiphyses, trabeculae, and matrix, to those described by Bernick and Hungerford (1965) in magnesium-deficient rats suggests that magnesium loss from bone, caused by excess vitamin D, might be a contributory factor.

Magnesium balance data were obtained in a series of balance studies (done over an eight-month period) in an infant with roentgenologic evidence of osteopetrosis but with biochemical evidence of hypophosphatemic rickets: marginal hypocalcemia, hypophosphatemia, and elevated serum alkaline phosphatase (Pincus *et al.*, 1947). Although the authors did not comment on the magnesium findings, analysis of their data shows that in the preliminary test period (at two and one-half months of age) the baby retained 10 times as much calcium as magnesium, and her calcium/magnesium absorptive ratio was 7/1. Two months after her vitamin D_2 supplementation was increased severalfold over the usual dose, her retention of calcium was 16 times that of magnesium, and she absorbed 10 times as much calcium from the gut. During the last balance period (at 10 months of age) when her mag-

nesium intake had been increased to 553 mg per day and her calcium intake had also been increased but proportionally less, the ratio of intestinal calcium to magnesium was 6/1. Her retention of Ca/Mg, however, was 9/1, a greater percentage of the absorbed magnesium being excreted in the urine. Her serum alkaline phosphatase had fallen by that time to hypophosphatasia-levels, her serum calcium remained marginally low, but her serum phosphorus had risen to 5.5 mg/100 ml. A trial of parathyroid extract transiently increased the serum calcium to within normal limits, and the serum phosphorus gradually fell to 3 mg. After 6 weeks, the child became refractory to parathyroid treatment. She died at 16 months, and her osteopetrosis was confirmed at autopsy.

Infantile hypercalcemia is associated with osteosclerosis. The first such patient reported was a dwarfed infant with hypercalcemia, cardiovascular and renal calcinosis, and mental retardation (Lightwood, 1932). What was then a rare syndrome appeared much more commonly in the literature in the 1950s, during an era of excessive fortification of milk with vitamin D in the British isles (Review: Seelig, 1969). The skeletal abnormalities were less commonly reported than was the severe cardiovascular, renal, and mental damage, which was termed the supravalvular aortic stenosis syndrome (SASS, Editorial, *Br Med J,* 1956). Fanconi and Girardet (1952) described an infant with the full syndrome. British babies were then reported with radiographic evidence of excessive deposition of sclerotic bone at the base of the skull, in periorbital bones, at ends of long bones, and at the borders of the vertebrae (Creery, 1953; Russell *et al.,* 1954; Dawson *et al.,* 1954; Lowe *et al.,* 1954; Stapleton and Evans, 1955; Schlesinger *et al.,* 1956; Joseph and Parrott, 1958). The amount of vitamin D estimated to be consumed by the affected children ranged from 1000 to 3200 IU, an amount that is not infrequently provided by the American diet. And, in fact, these lesions have not been limited to the British babies. The syndrome has been described in continental Europe and in America, the cardiovascular anomalies more frequently, the skeletal changes less frequently. Shiers *et al.* (1957) reported four children from one-and-a-half to almost five years of age, all of whom had roentgenologic evidence of osteosclerosis and other signs of hypervitaminosis D, but none of whom had histories of its excessive consumption. One had multiple bands of sclerosis parallel to the growing ends of the long bones, and distorted shafts; one had increased skull density, particularly at the base, with increased density of vertebral and carpal bones and of epiphyses, and one had rachitic-like lesions of the ends of the long bones but generalized osteosclerosis. The authors noted that the most heavily sclerosed bone had been laid down *in utero.* The oldest child, who was also hypothyroid, had very heavy osteosclerosis, particularly in the cranial and facial bones. All bones were affected, with bands of varying density. Three infants, who had been born prematurely, developed the classic signs of severe hypercalcemia by 6 months of age, and were found to have osteosclerosis at 10 to 17 months of age (Singleton, 1957; Daeschner and Daeschner, 1957; Snyder, 1958). None had been given more than 1000 IU of vitamin D as supplements (in addition to that provided by milk and other fortified foods). A Swiss child of low birth weight was born to a mother who later developed diabetes mellitus (a condition associated with low magnesium levels) and developed the full-blown syndrome by 5½ months of age after high-dosage vitamin D (Illig and Prader,

1959). Another infant who was small at birth, born to a mother who had taken 1000 IU vitamin D daily during much of her pregnancy, developed the syndrome at 4 months of age (Fraser *et al.*, 1966). Others, who developed the classic signs of hypercalcemia, SASS, and osteosclerosis at 9 to 18 months of age, were normal-sized at birth and had not been given high-dosage vitamin D supplements (O'Brien *et al.*, 1960; N. David *et al.*, 1962; Garcia *et al.*, 1964; D. Fraser *et al.*, 1966). The youngest infant with hypercalcemia and osteosclerosis had not had high-dosage vitamin D but had been given supplemental calcium (Wilkerson, 1964). Hyperreactivity to vitamin D is suspected in these children.

Infants and children have developed the complete hypercalcemic syndrome, including osteosclerosis, after massive intermittent doses of vitamin D (Amann, 1959; Manios and Antener, 1966). A child who had received excessive daily vitamin D supplements from his third through fifth years of age developed periarticular calcification and hypertension as well as osteosclerosis. He died, two years after his excessive supplements had been stopped, with renal failure and coronary atherosclerosis (DeWind, 1961).

Search for possible prenatal factors in the pathogenesis of infantile hypercalcemia and the SASS, led to studies of pregnant rabbits overdosed with vitamin D. W. Friedman and Mills (1969) found that some of the young had premature closure of the cranial bones, osteosclerosis, and palatal abnormalities similar to those seen in infants and children with infantile hypercalcemia and the SASS. Rowe and Cooke (1969), considering the role of maternal vitamin D in the genesis of the excessive fetal mineralization in the rabbits (W. Friedman and Mills, 1969; W. Friedman, 1968), commented that mothers of children with the SASS had not usually had histories of vitamin D overdosage during pregnancy. They noted that Friedman and Mills (1969) had considered the possibility of acquired decreased tolerance of vitamin D. They suggested that an infant who had undergone excessive mineralization *in utero* might be unduly susceptible to both hypercalcemia and osteopetrosis thereafter. It should be noted, here, that early studies of the effects of supplementing pregnant women with only moderate doses of vitamin D showed that the fetuses tended to have narrower cranial sutures and greater bone density than did the fetuses of control nonvitamin-D-supplemented mothers (Finola *et al.*, 1937; Brehm, 1937; Review: Seelig, 1978). Rowe and Cooke (1969) proposed that there might be a failure of regulating mechanisms for blood calcium in infants with SASS and osteosclerosis, and that there is probably a multifactorial basis for the difference in susceptibility to the disease. A factor that should be considered is the possible role of magnesium deficiency: gestational, magnesium malabsorption, or vitamin D induced. The ranges of susceptibility to vitamin D toxicity (Fanconi, 1956), and the magnesium loss caused by excess vitamin D should also be taken into account.

Intermittent magnesium treatment of the constipation characteristic of infantile hypercalcemia has been mentioned by some of the investigators of infantile hypercalcemia (Creery, 1953; Lowe *et al.*, 1954; Forfar, thesis). Stapleton and Evans (1955) noted that a hypercalcemic infant fed a formula free of calcium and magnesium exhibited a steady drop in serum magnesium levels (to 1.4 mEq/liter). Lowe *et al.* (1954) reported hypomagnesemia in a mild case and hypermagnesemia in a severe case. Metabolic balance studies of severely hypercalcemic infants showed

that they were in magnesium equilibrium (McDonald and Stapleton, 1955), only slightly positive (+ 1.3 mg/kg/day) or negative (Forfar, thesis). Fellers and Schwartz (1958), who studied two infants with severe hypercalcemia even when all vitamin D was removed from the diet, and who suggested that the disease is caused by abnormal vitamin D metabolism (Fellers and Schwartz, 1958b), reported that when calcium and vitamin D were deleted from the diet, the children went into strongly positive magnesium balance. These data suggest that magnesium deficiency may be part of this syndrome since infants should be in strongly positive magnesium balance (Seelig, 1964, 1971). Dalderup (1960) was the first to propose that magnesium deficiency might be contributory to this disorder.

The cited metabolic balance study by Pincus *et al.* (1947) supports the premise that magnesium malabsorption might be an initiating disorder that might contribute to hypophosphatemic rickets. Vitamin D, given to infants whose bone matrix is abnormal because of magnesium deficiency, might lead to hypermineralization, such as is produced in rats on high-dosage vitamin D plus calcium. The development of hypophosphatasia after 8 months of high-dosage vitamin D in the infant studied by Pincus *et al.* (1947), and the hypophosphatasia found in infantile hypercalcemia with hyperreactivity to vitamin D, suggest that intensification of magnesium deficiency by excessive vitamin D might be at fault, alkaline hypophosphatasia also being characteristic of magnesium deficiency.

However, once hypercalcemia is part of the clinical syndrome, it should be corrected before attempting to correct the magnesium deficiency with a parenteral magnesium load. Alkaline and pyrophosphatases (which destroy the calcification-inhibiting polyphosphates and pyrophosphates) are found, not only in bone but in the kidneys, cardiovascular, and other soft tissues. Since the phosphatases are magnesium dependent, administration of magnesium (in the face of hypercalcemia) might increase the risk of metastatic calcification, as had been suspected by the physicians who treated hypercalcemic infants *(supra vide).* Whittier and Freeman (1971) have provided experimental evidence that administration of magnesium to rats made hypercalcemic by hypervitaminosis D did in fact increase renal and myocardial calcification.

Congenital osteopetrosis need not be associated, however, with hypercalcemia. Rosen and Haymovits (1972) have reviewed the evidence that the disease is characterized by impaired bone resorption, and have speculated that a defect in lysosomal functions might be a significant factor in its pathogenesis. They demonstrated increased levels of the hepatic lysosomal enzyme, β-glycerophosphatase (the significance of which is unclear), and increased frequency of hepatic electron-dense mitochondrial particles. Whether these granules are comparable to those reported in myocardial mitochondria in magnesium deficiency and whether they are an indication of magnesium deficiency is speculative.

12.4.4.2. Magnesium/Calcitonin Interrelationships in Osteoporosis

In considering the effect of vitamin D and calcium supplementation to pregnant women, the active transport of calcium across the placental barrier and the effect of high calcium levels on calcitonin (CT) secretion should also be taken into

account. Acute hypercalcemia (in rats) has lowered the CT content of thyroid C cells (Gittes *et al.*, 1968), and has increased plasma immunoreactive CT levels in several species of animals (Littledike *et al.*, 1972). There is direct evidence that the hypercalcemia caused by excessive vitamin D (in cows) increases CT release (Young and Capen, 1970). In the gray lethal mouse, which develops osteopetrosis, it has been proposed that the primary lesion is hyperplasia of thyroid C cells, with overproduction of CT (D. Walker, 1965, 1966). There is evidence that CT not only inhibits bone resorption (Johnston and Deiss, 1966; Bélanger and Rasmussen, 1968; Raisz *et al.*, 1968; Baylink *et al.*, 1969; Hirsch and Munson, 1969), but that it also increases bone calcification, growth, and repair (Wase *et al.*, 1967; Pallasch, 1968; Ziegler and Delling, 1969; Delling *et al.*, 1970; Gaillard and Thesingh, 1968; Matthews *et al.*, 1972; Salomon *et al.*, 1973). Fetuses infused with calcium secrete CT (Littledike *et al.*, 1972; Garel *et al.*, 1973, 1974, 1976; Garel and Barlet, 1974) and the high fetal and cord CT levels are presumed to play an important role in normal bone growth and calcification (Samaan *et al.*, 1973, 1975). Thus, it seems likely that hypercalcemia of fetuses of mothers given excessive vitamin D might cause abnormally high fetal CT levels and increase bone mineralization. It is possible that low fetal magnesium levels, such as is postulated to be not uncommon, also increases CT secretion. The influence of the fetal magnesium/calcium ratios on the PTH/CT responses will influence the nature of the changes induced in fetal and infantile bone.

12.5. Other Genetic Bone Diseases and Possible Role of Magnesium

12.5.1. Osteogenesis Imperfecta

The similarity of the bone lesions in young of rats given excessive vitamin D during pregnancy to those of osteogenesis imperfecta, the magnesium depletion caused by hypervitaminosis D, and the infantile osteopenia and spontaneous fractures seen in infants likely to have magnesium deficiency *(supra vide)*, suggest that the magnesium status of members of families with osteogenesis imperfecta be explored. It is conceivable that familial malabsorption or renal wastage of magnesium might be contributory to the familial occurrence of osteogenesis imperfecta.

Whether osteogenesis imperfecta is a separate entity from the severe early form of hypophosphatasia, the bone lesions of which are indistinguishable from it, is not yet certain. The essential difference is in the serum phosphatase levels that have been reported. Hansen (1934) confirmed earlier reports that patients with osteogenesis imperfecta do not have the low serum alkaline phosphatase levels that are characteristic of hypophosphatasia. However, he analyzed tissues of a child who died of the disease, without having received unusual medication, and found almost complete absence of phosphatase in the periosteum and subperiosteal structures, where it is normally abundant. Solomons and Styner (1969) studied 28 patients (2 days to 14 years of life) with this disease and found the collagen biopsies

completely prevented mineralization at pH 7.4, and that pyrophosphatase in the presence of magnesium (3×10^{-3} M) markedly reduced the inhibition. Addition of magnesium without the enzyme partially reduced the inhibition of mineralization. They reported that bone from patients with osteogenesis imperfecta had much higher levels of pyrophosphate than did normal bone. This excessive pyrophosphate could be almost completely removed by *in vitro* treatment with pyrophosphatase plus magnesium. They also reported significantly higher than normal serum pyrophosphate levels in serum and urine, a finding not corroborated by R. Russell *et al.* (1971), who found higher than normal plasma levels only in hypophosphatasia. (The latter investigators, however, cautioned that plasma pyrophosphate levels might not be in equilibrium with that in bone or other tissues.) In view of the difference in pyrophosphate levels reported by the two groups, it is not possible to evaluate the significance of Solomons' and Styner's (1969) clinical report that administration of magnesium salts (2–6 mg/kg) to four patients with osteogenesis imperfecta lowered their serum and urine pyrophosphate levels toward the normal range.

J. Albright and Grunt (1971) studied magnesium balance (among other elements) in five children with osteogenesis imperfecta before and after fluoride treatment. All had negative magnesium balances, which were not affected by the fluoride. Riley and Jowsey (1973) treated three patients with magnesium oxide (15 mg/kg/24 hr) with only minor changes in bone formation and resorption, as measured by microradiography of iliac crest biopsies (Table 12-3). Whether the slight increases in bone formation and increases in bone formation and resorption noted in the two children with the severe form of the disease might have continued with prolongation of magnesium therapy would have been of interest. The older child, whose disease was less severe, and whose microradiographic studies showed less abnormal bone turnover, showed a drop in bone resorption (but still to within normal limits) but also a decrease in new bone formation. Intestinal and renal handling of magnesium should be correlated with bone response.

Benign hyperplastic callus formation, which simulates osteosarcoma, has been reported in patients with osteogenesis imperfecta. Banta *et al.* (1971) reviewed 21

TABLE 12-3. Effects of Magnesium Administration (15 mg/kg/24 hr) on Bone Resorption and Formation in Osteogenesis Imperfecta (Microradiography of Bone Biopsy)[a]

	Severe disease (multiple fractures)				Moderate disease (1 fracture/yr)		
	Patient 1 (4 yr old)		Patient 2 (4 yr old)		Patient 3 (8 yr old)		
Magnesium therapy	Before	After	Before	After	Before	After	Normal range
% Bone resorption	8.7 →	9.7	2.7 →	5.3	15.4 →	12.4	12–17
% Bone formation	3.7 →	6.7	1.8 →	2.7	4.6 →	2.3	12–17

[a] Adapted from Riley *et al.* (1973).

published cases, and 2 of their own, of such superabundant callus (usually of the tibia or femur but sometimes of the pelvis) that led to amputation for sarcoma in several instances. Replacement of muscle tissue by the extensive fracture callus was consistent with myositis ossificans. One of their patients (a young man of 22) also had bilateral dislocation of the radial heads and ankylosis of the spine. These abnormalities are noted because of the demonstration of exuberant growth of the femur, simulating osteosarcoma, of magnesium-deficient rats, and of the possibility that slipped epiphyses and chondrocalcinosis, including spondylitis, might be related to magnesium deficiency. Further evidence of abnormalities in collagen of patients with osteogenesis imperfecta derives from studies of skin collagen (Haebara *et al.*, 1969; C. Stevenson *et al.*, 1970; R. Smith *et al.*, 1975) and bone collagen and matrix proteins (Haebara *et al.*, 1969; Dickson *et al.*, 1975). Thin scleral collagen has been suggested as a factor in the characteristic blue sclerae. If the abnormality in bone matrix is similar to that produced by experimental magnesium deficiency (Bernick and Hungerford, 1965; Trowbridge and Seltzer, 1967), and if the propositus and his close relatives can be shown to absorb or retain magnesium abnormally, we might have another clue to the pathogenesis of this disease.

Another fragment of evidence that magnesium deficiency might be participatory is the aminoaciduria detected in some patients with osteogenesis imperfecta and in members of their families (Chowers *et al.*, 1962; Brigham and Tourtelotte, 1962; Summer and Patton, 1968). Five children with osteogenesis imperfecta were born to three families, almost all the members of which had aminoaciduria (Chowers *et al.*, 1962). The authors had investigated the amino acid excretory patterns of the families because of the frequent association between bone-wasting diseases and renal tubular dysfunction (e.g., osteomalacia, rickets, Fanconi syndrome, and hyperparathyroidism). Aminoaciduria has been produced in animals by experimental magnesium deficiency and is seen in patients with hyperreactivity to vitamin D (Fanconi and Girardet, 1952) or with intestinal malabsorption (Muldowney *et al.*, 1968), both conditions in which magnesium deficiency is demonstrable or suspected. Abnormal amino acid urinary output has been repeatedly demonstrated (Seelig and Berger, unpublished observation) in a woman with rapidly progressive osteoporosis, latent tetany of magnesium deficiency (Seelig *et al.*, 1975) and renal magnesium wastage (Seelig *et al.*, 1976/1980). The amino acid urinary excretory pattern of infants who have been given excessive vitamin D or who have hyperreactivity to vitamin D has rarely been reported. Drummond *et al.* (1964), however, ascertained that infants with familial hypercalcemia and nephrocalcinosis have abnormal tryptophan metabolism, termed the "blue diaper syndrome." This abnormality is of interest, since comparable abnormal metabolites of tryptophan are excreted in vitamin B_6 deficiency or abnormality, and pyridoxine enzymes are magnesium dependent (Review: Durlach, 1969b).

Osteogenesis imperfecta, like hypophosphatasia, abnormalities in vitamin D or magnesium metabolism, and congenital heart diseases that have been correlated with either or both of these metabolic abnormalities, can be isolated or familial. It is of interest that the bone and cardiac disorders have been seen in the same patient, sometimes in association with renal calcinosis. For example, Coleman (1959)

reported a baby with osteogenesis imperfecta, who died with nephrocalcinosis and thrombosis, among a series of 24 with infantile hypercalcemia, whose ECG changes (ST-T abnormalities) were not related to serum calcium levels. Examination of the ECG data shows similarities to those reported in conditions associated with magnesium deficiency (Review: Seelig, 1969a). It has been suggested that idiopathic hypertrophic subaortic stenosis might similarly be associated with hypercalcemia (McFarland *et al.*, 1978). Whether the growth retardation and skeletal abnormalities (particularly of the face and base of skull, leading to cardiofacies, and of the chest) that have been seen in cardiac outflow abnormalities (Chapter 4) are similarly mediated cannot be averred. Investigation of the metabolism of magnesium and of vitamin D of the propositus, and especially of infant siblings and mother, might provide insight into the etiology of these forms of combined cardiac and skeletal abnormalities.

It should be recalled that infantile hypercalcemia is frequently associated with the supravalvular aortic stenosis syndrome and with other cardiac outflow abnormalities. It is thus provocative that osteogenesis imperfecta has been reported in patients with aortic coarctation (Remigio and Grinvalsky, 1970) and in patients with valvular abnormalities requiring correction by open heart surgery (Criscitiello *et al.*, 1965; Heppner *et al.*, 1973; Wood *et al.*, 1973; Waters *et al.*, 1977). Perhaps most directly suggestive of the role of gestational magnesium deficiency in the pathogenesis of the combined congenital abnormalities of osteogenesis imperfecta, valvular disease, and aortic coarctation, are the two infants born with these disorders to a young woman who had had multiple pregnancies at short intervals (Remigio and Grinvalsky, 1970). They were the products of her ninth and tenth pregnancies, the seventh and eighth having terminated as spontaneous abortions. Such frequent pregnancies have been shown to be associated with maternal magnesium depletion. However, there might well have been a genetic predisposition to skeletal abnormalities, since the first two siblings had abnormalities of their hips. McKusick (1966) and Shoenfeld *et al.* (1975) have cited premature arteriosclerosis in osteogenesis imperfecta, another hint at possible underlying magnesium deficiency that is probably caused by defective ability to absorb or retain magnesium.

Hyperparathyroidism has also been associated with magnesium loss, and thus the coexistence of hyperparathyroidism and osteogenesis imperfecta tarda in women in their late forties or early fifties (Goldzieher *et al.*, 1957; Guay *et al.*, 1968; Salti *et al.*, 1973; Woolfson *et al.*, 1975) provides still another piece of circumstantial evidence linking magnesium deficiency with this form of osteopenia. Whether decreased estrogen secretion, which antagonizes parathyroid hormone activity, allows for an occult disorder to become overt in patients with mild forms of this disease is speculative.

Patients with osteopenias are commonly treated with high-dosage calcemic agents, which increase both magnesium loss and estraskeletal calcification. Thus, the combination of bone defects with damage to such organs as the heart, arteries, and kidneys, and ectopic calcification is explicable on the basis of a primary magnesium deficiency that increases susceptibility to toxicity of calcemic agents and ectopic calcification.

12.5.2. Hypophosphatasia

The term "hypophosphatasia" has been applied to the inborn error of metabolism that is characterized by defective bone mineralization, associated with low serum alkaline phosphatase activity, and high urinary output of phosphoethanolamine (Reviews: Fraser, 1957; Currarino, 1957). Most of the reports of this condition also indicate hypercalcemic values. No data have been found on magnesium levels, but there is reason to suspect that magnesium deficiency might be contributory to development of this syndrome.

Experimental magnesium deficiency causes low levels of alkaline phosphatase activity in bone, as well as in serum. Rats surviving few to 28 days of magnesium deficiency, and then repleted, had fragile bones thereafter (Duckworth *et al.*, 1940), such as are seen in adults whose hypophosphatasia is diagnosed late (Fraser, 1957). Low levels of bone alkaline phosphatase have been reported in patients with hypophosphatasia (Rathbun, 1948; Sobel *et al.*, 1953; Engfeldt and Zetterstrom, 1954; Schlesinger *et al.*, 1955; Currarino *et al.*, 1957). Without optimal amounts of alkaline phosphatase in bone, its mineralization is inhibited, since alkaline phosphatase is necessary for local destruction of mineralization inhibitors, such as polyphosphates and pyrophosphates. Additionally, high levels of phosphates intensify magnesium deficiency and have been correlated with increased tendency toward bone demineralization, possibly mediated by both mechanisms: (1) lowering of alkaline phosphatase levels caused by magnesium deficiency, and (2) exceeding the capacity of the phosphatase available to destroy the excess phosphates.

Osteopenia, associated with hypophosphatasia, has developed *in utero,* as well as in infancy, childhood, and adult life (Rathbun, 1948; Sobel *et al.*, 1953; Engfeldt and Zetterstrom, 1954; Schlesinger *et al.*, 1955; Fraser, 1957; Currarino *et al.*, 1957; Beisel *et al.*, 1960; Lessell and Norton, 1964; Pourfar *et al.*, 1972; Rudd *et al.*, 1976). The most severe form is among those whose clinical manifestations develop earliest, possibly beginning *in utero.* Extensive osteopenic lesions that are found at birth, or in the early months of life, resemble those of osteogenesis imperfecta. Affected infants are assumed to have had spontaneous fractures that healed imperfectly and with angulation (Fraser, 1957). Similar fractures have been reported among infants vulnerable to prenatal and early infantile hypomagnesemia, particularly those born to preeclamptic women and to immature mothers with frequent or multiple pregnancies. Intrauterine growth retardation of abnormal pregnancies and placentas might give rise to fetal hypomagnesemia that can play a role in bone dysplasia. Possibly contributory is vitamin D administration during pregnancy, which has been shown to increase placental scarring in women. Hypervitaminosis D in pregnant rats has been shown to damage the placenta and has been implicated in the bone damage of the pups: thin bones with abnormal osteoid and spontaneous fractures. The lesions, like those of early severe hypophosphatasia, were considered similar to those of osteogenesis imperfecta, and were speculated to have been caused by passage of excessive vitamin D to the fetus through the damaged placenta (Ornoy *et al.*, 1968, 1972). That excessive vitamin D can damage the osteogenic process, leading to lesions very much like those of severe early hypophosphatasia,

was shown in 1932 by Shelling and Asher. Young rats on a diet that increased susceptibility to vitamin D toxicity (low in calcium and high in phosphate) showed progressive demineralization and replacement of trabeculae by osteoid remnants and tiny fragments of calcified material when they were given excessive vitamin D for 26 days. It is conceivable that fetuses of pregnant women who are hyperreactive to vitamin D, who consume excessive phosphate-containing foods and beverages, and who are magnesium deficient are at particular risk of developing bone dysplasia.

Possibly the unexplained convulsions of infants with early severe hypophosphatasia (Rathbun, 1948; Fraser *et al.*, 1957; Currarino *et al.*, 1957) might also be of hypomagnesemic derivation, such infants probably having poor skeletal magnesium reserves to meet the requirements of early life (especially in those who are fed cows' milk). The infants commonly suffer from irritability, anorexia, and persistent vomiting, and among those surviving to the second year, craniostenosis develops (Fraser, 1957). These manifestations again focus on the possible role of abnormal response to vitamin D as a contributory factor. They are comparable to those of infantile hypercalcemia, associated with hyperreactivity to vitamin D (Review: Seelig, 1969b), in which low levels of serum alkaline phosphatase have also been reported (Lightwood, 1932; Fanconi and Girardet, 1952; Schlesinger *et al.*, 1956; Amann, 1959; Illig and Prader, 1959; Mitchell, 1960; Editorial, *Lancet,* 1960; O'Brien *et al.*, 1960; N. David *et al.*, 1962; Garcia *et al.*, 1964; Fraser, 1966). Among 14 patients with hypercalcemia, not of hyperparathyroid origin, N. David *et al.* (1962) recorded low alkaline phosphatase in five with vitamin D toxicity or hyperreactivity. Another similarity of hypophosphatasia and hypervitaminosis D is the development of band keratopathy (Lessel and Norton, 1964) and chondrocalcinosis (O'Duffy, 1970) in hypophosphatasia and in vitamin D toxicity (J. E. Howard and Meyer, 1948; Chaplin *et al.*, 1951, B. Andersen, 1956). In both hypophosphatasia and infantile hypercalcemia there is greater than normal susceptibility to vitamin D toxicity (Sobel *et al.*, 1953; Reviews: Fraser, 1957; Seelig, 1969b), but the skeletal abnormalities of hypophosphatasia have not responded to vitamin D therapy (Engfeldt and Zetterstrom, 1954; Fraser, 1957). It is speculated that magnesium deficiency might underlie both the susceptibility to vitamin D toxicity, and the vitamin D resistance of the hypophosphatasia syndrome. Magnesium has been protective against development of cardiovascular and renal lesions of vitamin D toxicity. Yet, in magnesium deficiency there is vitamin D resistance.

In view of the fact that vitamin D excess causes magnesium depletion, it is of interest that chondrocalcinosis has also been reported in patients with hypomagnesemia and in experimental magnesium deficiency and phosphate loading, as well as in hypervitaminosis D (Christensen *et al.*, 1951; DeWind, 1961). Vitamin D increases renal tubular reabsorption of phosphorus (Harrison and Harrison, 1941), as well as magnesium loss.

Nephrocalcinosis is common to hypophosphatasia (Review: Fraser, 1957), hypervitaminosis D (Review: Seelig, 1969b), and magnesium deficiency. The most notable difference between hypophosphatasia and infantile hypercalcemia is the osteopenia of the former and the osteosclerosis of the latter. It should be noted that vitamin D toxicity in animals on high intakes of calcium, and in children (most of

whose vitamin D is in milk, which is rich both in calcium and phosphate), tend to have hypermineralized bones. Vitamin D and its metabolites, however, have bone mineral-mobilizing activity, and vitamin D toxicity in adults is generally associated with osteomalacia. High phosphate intakes are also implicated in osteopenia.

Several additional similarities to abnormal findings of magnesium deficiency have been reported in hypophosphatasia. The teeth are irregularly calcified and tend to be lost prematurely, a finding attributed to inadequate growth of alveolar bone (Fraser, 1957). Comparable changes have been described in magnesium-deficient rats (Bernick and Hungerford, 1965; Trowbridge and Seltzer, 1967) and hamsters (Yamane, 1962, 1970), and both spontaneously and experimentally in several species of animals when given diets high in phosphates.

Children with hypophosphatasia, whose lesions become apparent after the age of six months, generally have less severe bone lesions. They are characterized by coarse metaphyseal trabeculae that are distorted and irregularly calcified. Bernick and Hungerford (1965) described comparable lesions in magnesium-deficient rats. Possibly the two brothers with epiphyseal irregularities and areas of long bone rarefaction, who had hypercalcemia and hypophosphatasia, and were diagnosed as a rare form of renal rickets because of excessive renal tubular reabsorption of phosphorus (Schneider and Corcoran, 1950), might have had abnormal metabolism of magnesium, vitamin D, or both.

High urinary output of phosphoethanolamine is characteristic of patients with hypophosphatasia (Fraser, 1957). In view of the foregoing correlations of findings of this metabolic disorder, with some of those of magnesium deficiency, it is of interest that magnesium deficiency has caused urinary excretion of phosphoethanolamine in a third of the animals in which this parameter was explored, and that several magnesium-deficient patients also had both low serum alkaline phosphatase levels and high urinary outputs of phosphoethanolamine (Pimstone *et al.*, 1966). An unpublished observation of high phosphoethanolamine excretion in a woman with latent tetany of magnesium deficiency (Seelig *et al.*, 1975) is of interest. In addition to excreting about 2½ times more than normal amounts of phosphoethanolamine, she also had low alkaline phosphatase levels following a trial period of 25-OH-D3 therapy, during which her serum magnesium fell further. Her magnesium deficit has not been reparable because she is a renal magnesium waster (Seelig *et al.*, 1976/1980).

12.6. Other Osteopenias Possibly Mediated by Magnesium Deficiency

12.6.1. Osteoporosis

There have been few studies on the influence of hormonal imbalances on bone magnesium accretion in postmenopausal osteoporosis, the most common cause of this disease. It has been estimated that no fewer than 6,000,000 have this disease in the United States (Harris and Heaney, 1969), even on the basis of the crude mea-

sure of osteoporosis provided by roentgenograms (which detects vertebral osteopenia only with loss of 30% to 50% of skeletal mass). The abnormalities in skeletal renewal that occur with metabolic bone disease and hormonal imbalances have been evaluated by Harris and Heaney (1969). Only those facets pertaining to possible mediating effects of magnesium loss in the hormonal imbalances are considered here. The available data suggest that magnesium loss from bone might contribute to several forms of osteoporosis.

Considering the effects of estrogen (and other female sex hormones), a deficiency of which has been most implicated in postmenopausal osteoporosis, and treatment with which has been and is under trial, there are fragmentary data that suggest that its effects on magnesium might be responsible for both promising and adverse effects. A clue to the retention of magnesium caused by estrogen was uncovered when analysis of metabolic studies showed that young women retain more of a marginal magnesium intake than do young men (Seelig, 1964). This observation was confirmed by Amiot *et al.* (1969) and Durlach (1970) in normal subjects and in patients with osteopenias. Comparable studies of magnesium retention of postmenopausal women have not been found. It was postulated that this difference in retention of magnesium might be a factor in the greater resistance of young women than men to cardiovascular disease (Seelig, 1964; Seelig and Lehr, 1971/1973; Seelig and Heggtveit, 1974), and might contribute to the increase in incidence of both cardiovascular and bone disease after the menopause (Seelig and Lehr, 1971/1973). On the other hand, plasma magnesium levels tend to be higher in young men than in young women, particularly during the period of greatest estrogen secretion, or when they are taking oral contraceptives (Dahl, 1950; N. Goldsmith, 1963; N. Goldsmith and Goldsmith, 1966; N. Goldsmith and Baumberger, 1967; DeJorge *et al.*, 1967; Durlach, 1970; N. Goldsmith *et al.*, 1970; Olatunbosun *et al.*, 1974; 1976/1978; N. Goldsmith and Johnston, 1976/1980). Durlach (1970) cautioned that this effect of estrogens might contribute to thromboembolic phenomena, and recommended that women on oral contraceptives be given magnesium concomitantly to prevent increased coagulability that might be caused by lowered plasma magnesium levels. N. Goldsmith and Johnston (1976/1980) have reviewed the evidence as to the risk of thromboembolism in women on oral contraceptives.

Estrogen exerts both direct and indirect effects on bone metabolism. It inhibits bone resorption *in vitro* (P. Stern, 1969) and increases endosteal bone formation in mice (M. Silverberg and Silverberg, 1941), but decreases calcium accretion in rats, even though it decreases bone resorption (Lindquist *et al.*, 1960). Estrogens antagonize PTH-induced bone resorption (Ranney, 1959; Nordin *et al.*, 1970; Atkins *et al.*, 1972), and in ovariectomized rats the bone-resorptive effect of PTH is increased (Orimo *et al.*, 1972). Since PTH mobilizes bone mineral (including magnesium), estrogen has increased bone uptake of magnesium (N. Goldsmith and Baumberger, 1967), and magnesium deficiency causes osteopenia, it is possible that at least part of the effect of estrogen on bone might be mediated by its effect on bone magnesium levels. Another bit of evidence that implicates magnesium loss in some of the osteopenic processes is the degranulation of mast cells in magnesium deficiency (Hungerford and Karson, 1960; Bois, 1963), a process that causes release of heparin as well as histamine. Heparin enhances the resorptive response of bone to PTH (Gold-

haber, 1965). Increased bone sensitivity to PTH has been implicated in osteoporosis, even in the absence of elevated endogenous PTH levels (Heaney, 1965; Harris and Heaney, 1969). Further support for this concept has been provided by Bélanger *et al.* (1975), who confirmed the damage to mast cells caused by magnesium deficiency, showed that female rats are more susceptible to magnesium deficiency-induced mast cell damage than are males, and that estradiol in the females and testosterone in the males resulted in less mast cell depletion.

Thus, there are data, deriving from magnesium-deficiency studies, that bear on some of the mechanisms that might be involved in the clinical benefit that has been reported with long-term prophylactic use of estrogens in postmenopausal women. Henneman and Wallach (1957) reviewed the records of 200 patients given estrogens by Albright and his colleagues for 1 to 20 years and found that, using loss of height as an index of osteoporosis, the use of estrogen arrested further loss of height in those already suffering from the disease, and prevented height loss in those whose postmenopausal estrogen treatment had begun before there was evidence of osteoporosis. [In regard to the concern about estrogen increase of cancer, the authors commented that in this group of 200 patients, who were given intermittent (cyclic) therapy, the incidence of carcinoma of the breast, cervix, and endometrium was low.] Determination of the effect of estrogens on bone thickness by means of densitometry has also shown estrogens to inhibit progression of postmenopausal osteoporosis (Meema and Meema, 1968; M. E. Davis *et al.*, 1966; Meema *et al.*, 1975; N. F. Goldsmith and Johnston, 1975,1976/1980). Estrogen has also been shown to decrease bone resorption, as measured by urinary output of hydroxyproline (Riggs *et al.*, 1969; Gallagher and Nordin, 1972) and to be effective (in doses of no less than 1.25 mg of conjugated estrogen in a series of 220 severely osteoporotic women) in arresting vertebral fractures (Gordan, 1971). The mechanism of action has been postulated to be via estrogen inhibition of PTH-induced bone resorption in postmenopausal women (Nordin, 1971; Gallagher and Nordin, 1972; Seelig and Lehr, 1971/1973).

Why women are more susceptible than are men, in the middle years, to (presumed) relative hyperparathyroidism is not clear. It is possible that the estrogen-induced lowering of plasma magnesium (which might be the result of a shift to intracellular sites) might result in chronic stimulation of parathyroid secretion. If such stimulation causes parathyroid hyperplasia [as Larvor *et al.* (1964a) have demonstrated in calves], when the ovaries cease functioning the overactive parathyroids might continue to mobilize bone minerals, excessively in the absence of the counteracting effect of estrogen (Fig. 12-6).

The later development of osteoporosis in men probably reflects their longer gonadal activity. Testosterone has also been shown to have activity in clinical osteoporosis (Gordan, 1954).

Evidence that calcitonin (CT) retards disuse osteoporosis (Hantman *et al.*, 1973) and that magnesium administration stimulates CT secretion suggests that magnesium administration may be useful in this form of osteoporosis. It recalls the work with rats, showing interrelationships among magnesium, CT,PTH, and cortisone (Palmieri *et al.*, 1969; Eliel *et al.*, 1971). Cortisone, an excess of which has long been known to cause osteoporosis, abolished the hypomagnesemic effect of

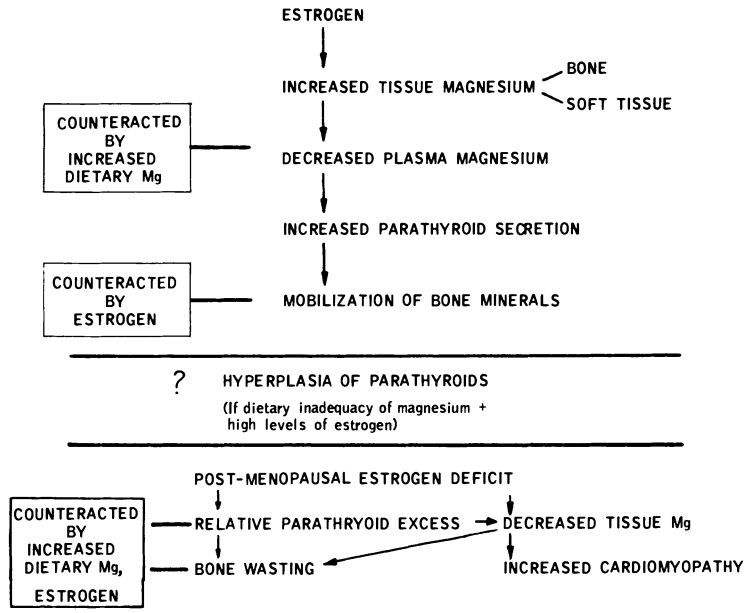

FIGURE 12-6. Possible estrogen/parathyroid/magnesium interrelations affecting bone and soft tissues.

CT, an effect attributed to its interference with CT inhibition of bone-resorption. On the other hand, patients with regional enteritis had their magnesium deficiency (to the point of hypomagnesemia) intensified by corticosteroid therapy (Gerlach *et al.*, 1970). Although only the acute signs of magnesium deficiency were considered in that paper, it should be recalled that malabsorption is implicated in osteopenia (i.e., celiac rickets and osteomalacia), as are corticosteroid therapy and magnesium depletion.

Administration of magnesium supplements to several patients, including a few with conditions (e.g., alcoholism or cirrhosis) that predispose to magnesium deficiency, improved their calcium retention (Briscoe and Ragan, 1966). Du Ruisseau

TABLE 12-4. Effect of Calcium Therapy on Magnesium Balance in Osteoporosis and in Hypercalciuria[a]

Disease	Number	Mean increase in daily loss of Mg (mg)
Osteoporosis (common immobilization)	6	9
Osteoporosis (idiopathic)	6	15
Osteoporosis (corticosteroid)	6	57 (↑ fecal Mg)
Hypercalciuria	6	148 (↑ urinary Mg)

[a] Adapted from R Parlier, D Hioco, and R Leblanc, *Rev Franc Endocr Clin* 4:93–135, 1963.

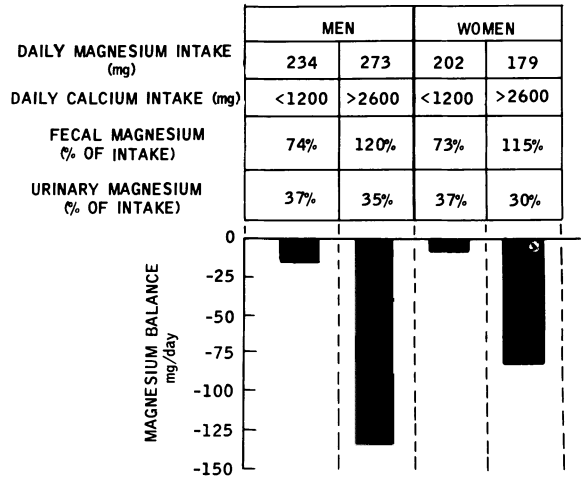

FIGURE 12-7. Effect on magnesium balance of calcium supplementation in patients with osteopathies. (Adapted from Amiot *et al.*, 1969; in Seelig, 1971.)

and Marineau (1971/1973) showed that patients with osteopenia retained more calcium when supplemented with magnesium. In contrast, administration of calcium to such patients increased their magnesium deficit (Table 12-4, Fig. 12-7, Parlier *et al.*, 1963; Amiot *et al.*, 1969).

12.6.2. Renal Osteodystrophy

The osteopenia seen in patients with uremia, whether they are dialyzed or not, entails complex interrelationships among etiologic and complicating factors; space does not permit their consideration here. Selected from the massive literature on this subject are data directly or indirectly bearing on the possibility that tissue magnesium depletion might play a role. Serum magnesium levels are unreliable as an index of the magnesium status of uremic patients. High normal, and low levels have been reported that are unrelated to tissue levels (Lim *et al.*, 1969a; Lim and Jacob, 1972c). Metabolic balance determinations are also unreliable, the equilibrium reported by Clarkson *et al.* (1965) being associated with subnormal intestinal magnesium absorption that balanced its subnormal urinary excretion. In contrast, patients with chronic renal failure receiving low protein diets, lost as much as 139 mg of magnesium daily, despite slightly elevated serum magnesium levels (Kopple and Coburn, 1973).

Massry and Coburn (1970a) proposed that tissue magnesium deficiency in patients with progressive renal failure (even when serum magnesium levels are elevated) might be contributory to their hypocalcemia, vitamin D resistance, and defective response of the skeleton to parathyroid hormone. On the other hand, if the tissue magnesium deficit involves the parathyroids, secondary hyperparathyroidism might ensue. Pletka *et al.* (1971) have, in fact, shown that the levels of

parathyroid hormone (PTH) of patients treated by hemodialysis with water containing 1.5 to 2.5 mEq of magnesium per liter fell 20% from pretreatment high levels. Those who were hemodialyzed with water containing low concentrations of magnesium (0.5 mEq/liter), who had lesser initial elevations of PTH, showed a 118% rise in PTH after two months of treatment. It is well known that patients being treated by dialysis are subject to hyperparathyroidism, with the attendant problems of bone loss and metastatic calcification (Buckle, 1970; Kleeman *et al.*, 1970; Genuth *et al.*, 1970; Danesh *et al.*, 1970; Terman *et al.*, 1971; Henderson *et al.*, 1971; Editorial, *Brit. Med. J.*, 1972; Arora *et al.*, 1975). Cardiovascular involvement is common, and cardiovascular disease is by far the leading cause of death in patients on chronic dialysis (Lowrie *et al.*, 1974), accelerated arteriosclerosis (Lindner *et al.*, 1974; Curry and Roberts, 1977), myocardial calcification, and heart block having been reported.

There is concern about producing hypercalcemia and possibly hypermagnesemia by using untreated hard water (Freeman *et al.*, 1967). Acute symptoms of hypermagnesemia (blurred vision, flushed face, weakness, and inability to stand) were produced by use of a dialysate containing 15 mEq of magnesium per liter (Govan *et al.*, 1968). Posen and Kaye (1967) have reported that magnesium levels in the dialysis bath water in major centers range from almost 0 to 0.8 mEq/liter, usually depending on the concentration in the water supply; although they used Montreal water (one of the harder water supplies available), they added 1 mEq of magnesium to each liter, so as to provide 1.65 mEq/liter. They attribute to the added magnesium the freedom of their patients from metastatic calcification over the four-year observation period. They did not comment on the incidence of osteodystrophy, but Catto *et al.* (1973) commented that osteodystrophy is not a problem in Montreal or London (both hard-water cities), whereas it is in Newcastle and Los Angeles. Kleeman *et al.* (1970), who commented on the magnesium supplied by two medical centers in Los Angeles, 0.5 and 1.5 mEq/liter, suggested that providing a dialysate magnesium concentration (1.5 mEq/liter) sufficient to prevent hypomagnesemia might reduce the tendency toward metastatic calcification and secondary hyperparathyroidism. This recommendation was also made by Danesh *et al.* (1970). It may be relevant that the accelerated arteriosclerosis reported by Lindner *et al.* (1974) was from a center in Seattle, a soft-water area. The low incidence of osteodystrophy in two hard-water cities (Catto *et al.*, 1973) suggests that the magnesium provided might also protect against secondary hyperparathyroidism and osteodystrophy.

However, there is no consensus as to the optimal magnesium concentration of water used for dialysis. Unlike Posen and Kaye (1967), who added magnesium to the hard water, it is common to attempt to bring the serum magnesium levels down to normal limits by using dialysates with low magnesium concentrations (from 0.16 to 1.0 mEq/liter) (Johny *et al.*, 1971; W. K. Stewart and Fleming, 1971; 1973; Paschen *et al.*, 1971). In one reported patient receiving twice-weekly hemodialysis with water containing 0.8 mEq/liter of magnesium, severe hypomagnesemic cramps developed that promptly responded to magnesium therapy (Triger and Joekes, 1969). In view of the cited evidence that tissue levels of magnesium can be low in patients with renal disease, despite high serum levels, and the importance of tissue

magnesium in protecting against pathologic changes in cardiovascular and skeletal tissues, the advisability of depleting the body magnesium by use of low magnesium-dialysate is open to question.

Since bone and serum magnesium tend to be in equilibrium, the fact that surface bone magnesium levels of uremic patients tend to be higher than normal (Contiguglia *et al.*, 1972; Alfrey and Miller, 1973) is not surprising. Its significance is uncertain. Alfrey and Miller (1973) found that 30% of the bone magnesium of uremic patients with hypermagnesemia is within the bone hydration shell or on the crystal surface, and speculate that, since magnesium can influence crystal size and stability, an excess might play a role in osteodystrophy. They noted, however, that the deeper magnesium is not as readily exchanged, and its mobilization is dependent on the resorptive process. However, chronic experimental uremia adversely influences collagen metabolism in both skin and bone (Hahn and Avioli, 1970). Also, experimental magnesium depletion causes formation of abnormal bone matrix with defective calcification capacity. Thus, it seems likely that loss of deep-located bone magnesium should have a more significant effect on the osteopenia of renal disease than the gain at the surface.

A final indirect bit of evidence that magnesium deficiency might contribute to renal dystrophy is the observation that renal osteodystrophy is rare in Israel (Berlyne *et al.*, 1973b). The rarity of this disease (in Beer Sheva) was attributed by the investigators to the low phosphorus intake of dwellers in that area. However, in another publication, Berlyne *et al.* (1973a) reported that the water in that area was also very high in magnesium and calcium.

12.7. Joint Diseases Possibly Mediated by Magnesium Deficiency

12.7.1. Osteochondrosis

There are meager clinical data that suggest that magnesium deficiency might play a role in osteochondrosis or osteochondritis (Legg-Perthes disease; slipped epiphyses). J. F. Miller (1944) reported a child who had had neonatal tetany and hyperirritability and cyanotic episodes during the early weeks of life, for which he was given calcium therapy, which was continued (with halibut liver oil) from then on. By 6 months of life he developed normocalcemic convulsions that stopped at the age of one; his tremors persisted. At 3½ years of age he had osteochondrosis of the capital epiphysis of the left femur, including fragmentation and flattening of the epiphysis. At that time he had hypercalcemia (12.9 mg/100 ml). By the age of 6 years, in addition to dizziness and tremors, he had developed muscle cramps and carpopedal spasms, at which time his plasma magnesium was determined for the first time; it was 1.4 mEq/liter. He responded strikingly to magnesium therapy (300 mg $MgSO_4$ three times daily), with disappearance of tremors and dizziness. After the supplements were stopped by his parents for a week when he suffered an attack of bacillary dysentery, his tremors and dizziness recurred, he had positive Trous-

seau and Chvostek signs, and his plasma magnesium dropped to 0.5 mEq/liter. He again improved promptly on magnesium therapy. The osteochondrosis had been treated surgically, and thus the effect of the magnesium therapy on this disease could not be ascertained, but Miller speculated that there might have been a relationship between the boy's probable early magnesium deficiency and his epiphyseal abnormality. Klingberg (1970) reported mild osteochondritis of shoulders, knees, and hips (Legg-Perthes-like) in a boy who suddenly developed a carpopedal spasm of 6 hours duration at 5 years of age and who was found to have both hypomagnesemia (0.8 mEq/liter) and hypokalemia (2.8 mEq/liter). A 6-day metabolic balance study showed minimal negative magnesium balance; supplementation with 60 mEq magnesium (as the acetate) produced a slightly positive magnesium balance (+42 mEq); he continued to excrete 5–9 mEq/day in his urine. After 6 months of magnesium supplementation, the patient's bony lesions reverted to almost normal. With the lower magnesium supplements, his tetany recurred. The possibility of a renal tubular defect in magnesium reabsorption was proposed as an explanation of the child's high magnesium requirement. Follow-up of this child for 6 years has shown persistence of his renal wastage of magnesium. He has also developed cardiac and skeletal abnormalities (W. G. Klingberg, personal communication, 1978). Children with hypophosphatasia (proposed as related to magnesium deficiency) also have metaphyseal and epiphyseal abnormalities, as have some children with vitamin-D-refractory rickets, also related to magnesium deficiency.

The studies that show abnormalities of metaphyseal trabeculae and of the epiphyseal cartilage and ground substance (Yamane, 1962; 1970; Yamane and Singer, 1953; Bernick and Hungerford, 1965; Clark and Bélanger, 1967; Trowbridge and Seltzer, 1967; Trowbridge, 1971) provide direct evidence that experimental magnesium deficiency causes abnormalities in epiphyseal structure. Abnormal epiphyseal cartilage and diaphyses have also been seen in pups of pregnant rats overdosed with vitamin D (Ornoy *et al.*, 1972), and cessation of epiphyseal osteogenesis in young rats with vitamin D toxicity (Shelling and Asher, 1932; Ham and Lewis, 1934; Storey, 1960), lesions that might reflect secondary magnesium deficiency.

Before a generalization can be drawn (correlating clinical epiphyseal disease with early magnesium deficiency), there should be evaluation of children with this disease, and of their families, for abnormalities in magnesium absorption and retention.

12.7.2. Chondrocalcinosis and Osteoarthritis

Enlargement of the joints and marked stiffness were identified as signs of magnesium depletion in calves and were shown to resolve when magnesium salts were added to a high-phosphate, low-calcium diet by Huffman *et al.* (1930). Deletion of the magnesium carbonate supplement resulted in recurrence of the stiffness within two months. Cattle foraging in low-magnesium areas also developed articular damage, in these instances characterized by erosions of the cartilage (Willers *et al.*, 1965). House and Hogan (1955) demonstrated that optimal intakes of magnesium (0.35% of diet) and potassium (1.5% of diet) prevented the stiffness and periarticular deposition of calcium phosphate that developed in magnesium-deficient guinea pigs

receiving only slightly more phosphorus than calcium (P/Ca = 0.9/0.8%) (Hogan *et al.*, 1950). Joint stiffness was worst in guinea pigs fed rations containing 1.7% phosphorus, 0.9% calcium, 0.04% magnesium, and 0.41% potassium.

Chondrocalcinosis has also been associated with human diseases associated with magnesium loss. The first instances were in rheumatoid arthritis patients taking excessive amounts of vitamin D (Review: Christensen *et al.*, 1951). Additional to the metastatic calcification of the arteries, kidneys, and other viscera, there was sometimes marked and disabling calcification of the periarticular structures, involving the synovial cavities, bursae, and tendon sheaths (accompanying generalized osteoporosis). Withdrawal of the toxic vitamin D supplements resulted in decreased periarticular calcification. This condition was usually seen among rheumatoid arthritis patients who had self-medicated themselves with vitamin D supplements providing as much as 200,000 units daily. It was also seen in a child who had been given high dosage (> 40,000 units/day) vitamin D since the age of three because of suspected rickets, diagnosed on the basis of a "peculiar feeling to the skull," as well as wrist changes. When seen by the investigator (DeWind, 1961) at 5½, he had periarticular calcification, as well as osteosclerosis that encroached on the medullary canals. The bone changes resemble those described in experimental magnesium deficiency.

A patient with monoarticular osteoarthritis, whose hypophosphatasia was diagnosed in middle age, had calcification of the articular cartilage of her hips, symphysis, and arthritic knee (O'Duffy, 1970). This was the first time note was taken of the deposition of calcium pyrophosphate in cartilage of a patient with hypophosphatasia, but O'Duffy reviewed the literature and found several additional cases in which periarticular calcification was noted in the case reports. He reviewed some of the metabolic disorders in which pseudogout was reported, and found that it was common in hyperparathyroidism. McCarty *et al.* (1974), who compared the frequency of concomitant chronic diseases in patients with pseudogout and in those with osteoarthritis of the large weight-bearing joints, found no significant differences, and that immunoreactive parathyroid hormone was elevated in both groups. They postulate that sustained low-grade hyperparathyroidism might be related to the genesis of the articular lesions. This is a provocative observation, since both vitamin D excess and hyperparathyroidism are associated with loss of magnesium. McCarty (1974) and his co-workers (McCarty *et al.*, 1971) have related magnesium with inhibition of calcium pyrophosphate precipitation in synovial fluid, correlating this effect with magnesium-activation of pyrophosphate transphosphorylase.

Precipitation of calcium pyrophosphate in the joints of patients with hypomagnesemia has been reported. McCarty *et al.* (1974) reported one such instance in a patient with psoriasis. Runeberg *et al.* (1975) reported a young man who had renal tubular magnesium wasting, hypomagnesemia, and from whose knee joint calcium pyrophosphate crystals were obtained. This patient is of particular interest, since he had had nephrocalcinosis from the age of seven, following calcium therapy of his convulsive hypocalcemia, and developed ECG changes similar to those seen with magnesium depletion when he was 14 years of age. After he retained 247 mmol of magnesium (during a period of intravenous infusions of 40–60 mmol of magnesium chloride daily for 8 days), he was maintained on high oral magnesium dosage (20 mmol

as Mg $(OH)_2$ and 30 mmol as $MgCl_2$) and potassium for 2 years. His joint effusion disappeared and he remained symptom-free since. Rapado and Castrillo (1976/1980b) reported a man of 38 with knee joint pain and swelling of several years duration, who also had renal tubular magnesium wasting and hypomagnesemia. He had X-ray evidence of linear calcification of the cartilage, and biochemical demonstration of calcium pyrophosphate in a synovial biopsy. This patient, too, responded to magnesium therapy, but his response is not as clear-cut because he was maintained also on antiinflammatory drug therapy.

Ankylosing hyperostosis, a common disorder of the middle-aged and elderly that affects the spine and large joints, has also caused calcaneal spurs (particularly of the heel), and has also been associated with precipitation of crystals of calcium pyrophosphate dihydrate. Among 30 patients reported by Utsinger *et al.* (1976), one had hypomagnesemia, three had hyperphosphatemia, and four had elevated serum alkaline phosphatase. More intensive study of the magnesium status should yield useful data.

Complicating the problem of chondrocalcinosis and exostosis and their response to magnesium is pyrophosphate's inhibition of precipitation of calcium phosphate compounds in urine (Fleisch and Neuman, 1961; Fleisch and Bisaz, 1962a), and the necessity of pyrophosphatase for normal (bone) mineralization. Thus, there must be a delicate balance between enzymes and substrate on the one hand, and concentrations of the minerals: magnesium, calcium, and phosphorus on the other. Hydroxyapatite crystals are most commonly found in periarticular disease, in contrast to the calcium pyrophosphate dihydrate that is more frequent in intraarticular disease, such as is not uncommon in uremia (Parfitt, 1969). Mirahmadi *et al.* (1973) reported that calcium hydroxyapatite has precipitated periarticularly in renal failure patients undergoing hemodialysis: They suspect that hyperphosphatemia is the most likely provocative factor. They noted that none of their seven patients with this complication had magnesium depletion, and recommended measures to lower the serum phosphate levels and use of higher calcium concentrations in the dialysate, to suppress parathyroid secretion. Since increased magnesium also suppresses the parathyroid function, further study and individualization of the prophylactic or therapeutic regimen is advisable.

Ankylosing spondylitis, accompanying bone resorption (from adolescence on), and irregularity and erosion of the articular cartilage (such as has been reported in magnesium deficiency, *supra vide*), with obliteration of the joint space, has been encountered in primary hyperparathyroidism (Bunch and Hunder, 1973), a condition associated with magnesium loss.

Articular lesions—peri-, para-, and intraarticular calcification—have also been seen in uremic patients (Review: Parfitt, 1969). An unusual paraarticular lesion occasionally seen in such patients, and that had been more common when high doses of vitamin D were given as treatment for arthritis (Christensen *et al.*, 1951) is tumoral calcinosis, rubbery or cystic calcific mass. McPhaul and Engel (1961) reported two patients with this disorder in one family, four of whom—including the patients—had low plasma alkaline phosphatase levels. Parfitt (1969), who reviewed the factors involved in soft tissue calcinosis of uremia (including the articular forms

of calcification), considers hyperphosphatemia the most important single factor, and calciphylaxis (produced by prior "sensitization" with vitamin D or parathyroid hormone) as a unifying hypothesis. Since Selye, who promulgated the calciphylaxis theory, found magnesium to be protective (against cardiorenal calcinosis caused by high phosphate, vitamin D, or PTH), perhaps low magnesium levels caused by these agents (as well as by uremic acidosis) might play a role in the abnormal calcification processes of the joints in uremic patients. Whether magnesium deficiency also plays a role in osteoarthritis cannot be averred in the absence of other than the meager animal and clinical data available.

Leonard and Scullin (1969) and Leonard *et al.* (1971) have proposed that in soft tissue, where the concentration of magnesium exceeds that of calcium, the formation of MgATP inhibits calcium apatite formation. This group has demonstrated that the local magnesium/calcium ratio influences calcification of tendons (in turkeys) and that egress of magnesium precedes the onset of calcification (Leonard *et al.*, 1976). This is a physiologic maturation process in turkey tendon. It seems plausible that low Mg/Ca concentrations in soft tissues, and in articular and periarticular tissues, might similarly participate in calcification, and that a higher magnesium concentration might inhibit it.

12.8. Magnesium Deficiency and Dental Disorders

Damage to teeth, as well as to bones and to soft tissues, were among the findings reported from the earliest magnesium deficiency studies. Kruse *et al.* (1932) found that rats surviving severe magnesium deficiency for 10 weeks had loose molars and incisors. Further data on the abnormal periodontal soft tissues were provided by H. Klein *et al.* (1935). Brittle, chalky teeth (loose in their sockets) were noted by Watchorn and McCance (1937) in subacute magnesium-deficient rats. They, like H. Klein *et al.* (1935), found striations in the dentin, suggestive of intermittent interference with the calcification process; they also reported odontoblastic degeneration. Becks and Furata (1939, 1941) reported pronounced degenerative changes in the enamel epithelium of rats by the 72nd day of subacute magnesium deficiency. Irving (1940) confirmed the damage to the enamel, caused by magnesium deficiency, as well as striations in the dentin. He also noted increased width of the predentin above the basal portion of the teeth that he considered unique to magnesium deficiency. Yamane and Singer (1953) found alternate bands in the incisors of magnesium-deficient hamsters that were associated with odontoblastic degenerative changes, and decreased width of the enamel-forming cells (Yamane, 1962). Bernick and Hungerford (1965) showed that magnesium-deficient rats had disturbed dentin calcification. It was characterized by a wide uncalcified zone separated from the predentin by a thin calcified line. There was also odontoblastic degeneration. Trowbridge (1971) and Trowbridge *et al.* (1971) point out that magnesium deficiency also causes dentinal striations and that the incisal dentinal striations ceased within four days of magnesium supplementation; thereafter the new dentin was normal except in areas adjacent to enamel, where it was somewhat attenuated.

The importance of magnesium for the metabolism of teeth is suggested by the avidity of teeth of control magnesium-deficient lambs for ^{28}Mg (McAleese *et al.*, 1961). E. R. Morris and O'Dell (1961) had shown that increasing the phosphorus content of the diet from 0.4 to 1.7% did not affect the calcium or phosphorus content of the teeth but intensified magnesium deficiency, which they had earlier shown to cause formation of the defective teeth and decay; the teeth were loose in their sockets (O'Dell *et al.*, 1960). The authors commented that their findings suggested that the magnesium deficiency probably affected cell function and development of the organic matrix of the tooth, rather than its mineralization. That the organic matrix of dentin of magnesium-deficient rats did, indeed, differ from that of controls was demonstrated by Bernick and Hungerford (1965). Differences in staining characteristics suggested that the ground substance of the matrix of bones and teeth of magnesium-deficient rats contained less polymerized mucopolysaccharides; they are thus less subject to normal calcification. Defective dentin matrix formation by acutely magnesium-deficient rats was confirmed by Trowbridge and Seltzer (1967). They demonstrated greatly reduced tritiated proline labeling in the organic matrix of the dentin and retarded dentin formation and calcification, arrested appositional bone growth and resorption of the crest of the alveolar process (Trowbridge and Jenks, 1968; Trowbridge, 1971). The periodontal ligament was wider in the magnesium-deficient rats than in the controls, and there was minimal osteoblastic activity and lesser evidence of alkaline phosphatase activity in the pulps and the serum of the deficient rats. Magnesium-deficient hamsters also had periodontal abnormalities, as compared with pair-fed controls (Yamane, 1962, 1970). The periodontal ligament was disorganized, calculi formed in the gingival sulci, and the interdental bony septum showed resorption. Following extraction of teeth, the magnesium-deficient hamsters exhibited delayed healing, an effect attributed to impaired matrix formation. Delayed eruption of the permanent teeth, as well as abnormal mineralization of both dentin and enamel, odontoblastic degeneration, arteriosclerosis of pulpal vessels, and pulpal calcification were reported by Binus (1968) in magnesium-deficient dogs.

Two genetic clinical abnormalities that the author postulates may be associated with magnesium depletion: hypophosphatasia (Reviews: Fraser, 1957; Currarino *et*

TABLE 12-5. Dental Signs in Pseudohypoparathyroidism and in Idiopathic Hypoparathyroidism[a]

Abnormality	Pseudohypoparathyroidism (40 cases)	Idiopathic hypoparathyroidism (50 cases)
Dental hypoplasia	5 (12%)	3 (6%)
Enamel defects	4 (10%)	9 (18%)
Unerupted teeth	13 (33%)	9 (18%)
Root defects	7 (17%)	2 (4%)
Thick lamina dura	1 (2½%)	3 (6%)

[a] Derived from Bronsky *et al.* (1958).

al., 1957) and pseudohypoparathyroidism (Review: Bronsky *et al.*, 1958) are associated with dental disorders that bear some resemblance to those of experimental magnesium deficiency. In hypophosphatasia irregular calcification and severe caries have been reported. Three quarters of the children whose disease became manifest by the sixth month of life had premature loss of teeth, attributed to inadequate growth of alveolar bone and incomplete formation and early resorption of the roots of the teeth (Review: Fraser, 1957; Pourfar *et al.*, 1972). Beisel *et al.* (1960) reported early loss of all permanent teeth of a patient who presented his first signs of hypophosphatasia as an adult. Both in pseudohypoparathyroidism and in idiopathic hypoparathyroidism, comparable dental abnormalities are not uncommon (Table 12-5) (Bronsky *et al.*, 1958).

It is noteworthy that in two conditions with abnormal vitamin D metabolism, dental abnormalities have been reported. Children with hyperreactivity to vitamin D, who also have hypophosphatasia, have a high incidence of malocclusion, enamel hypoplasia, and severe caries. Rampant caries, necessitating early extraction of all teeth (before the age of 20) has been reported in a patient with familial hypophosphatemic vitamin-D-resistant rickets (Blackard *et al.*, 1962). Enamel hypoplasia involving teeth that calcify after birth was found in members of a family with hypophosphatemic rickets and secondary hyperparathyroidism (Arnaud *et al.*, 1970). On the other hand, periodontal disease has been correlated with high phosphate intakes and secondary hyperparathyroidism and with osteoporosis (Lutwak, 1974; Review: Krook *et al.*, 1975).

13
Renal Damage Caused by Magnesium Deficiency

Metastic calcification, frequently involving the kidneys, is not infrequent in patients with hypercalcemia, whether of dietary or metabolic derivation, because of osteolytic processes, or as a result of therapy. The study by B. S. W. Smith and Nisbet (1968), which showed that magnesium-deficient rats develop nephrocalcinosis, and later osteoporosis, is an appropriate reference for the transition from bone damage to renal damage of magnesium deficiency.

13.1. Experimental Magnesium Deficiency

The diets contrived to be magnesium deficient are almost always imbalanced in other constituents as well. The early diets were usually rich in fats, calcium, phosphorus, and vitamin D, which were effective in producing acute signs of magnesium depletion rapidly (Kruse *et al.*, 1932) and also produced severe renal glomerular and tubular damage that was most extensive at the junction of the cortex and medulla (Cramer, 1932; Brookfield, 1934). Modifications of that diet (designed-specifically to produce hypercholesterolemia and atherosclerosis) also produced renal damage (Hellerstein *et al.*, 1957; Gottlieb *et al.*, 1959; Vitale *et al.*, 1959). There was deposition of calcium microliths in the lumina of the collecting tubules that was accompanied by tubular dilatation, and flattened epithelium. High dietary magnesium (96 mg Mg/100 g of diet) abolished the renal tubular calcification, regardless of the amount of calcium fed, in the animals not loaded with cholesterol and cholic acid, and decreased it in fat-loaded rats.

With less imbalanced diets, designed to produce subacute magnesium deficiency (Watchorn and McCance, 1937), rats developed occasional to more frequent calcareous deposits scattered throughout the renal cortex and medulla. Those with most severe damage had extensive calcareous casts and obliteration of the epithelium of the straight and collecting tubules, but no glomerular changes. Greenberg *et al.* (1938), also using a less imbalanced diet that did not produce signs of acute

deficiency and that contained neither excess phosphate nor very high doses of vitamin D, but was high in calcium (Tufts and Greenberg, 1937), found that prolonged magnesium deprivation of rats produced corticomedullary necrosis and calcinosis involving both the tubular cells and lumina. They attributed the renal calcinosis to the high calcium/magnesium ratio. Greenberg (1939) later attributed part of the severe manifestations of the magnesium-deficiency syndrome (including the renal calcinosis) in the early studies to the inadequacy of vitamins B_2 and B_6 in the vitamin-B-complex supplements then available. The concomitant magnesium and pyridoxine deficiencies might be relevant to calcium oxalate deposition in the kidneys, magnesium being a cofactor in vitamin B_6 metabolism (Review: Durlach, 1969b), oxalate excretion increasing in vitamin B_6 deficiency (Gershoff *et al.*, 1959), and a combination of high magnesium and vitamin B_6 being useful in decreasing calcium oxalate and apatite nephrocalcinosis and urolithiasis (Gershoff and Andrus, 1961; Gershoff and Prien, 1967). Gershoff and Andrus (1961) also showed that the amount of magnesium usually provided control rats (400 ppm) did not completely prevent formation of apatite salts in the kidneys. Tenfold higher intakes were completely protective.

Most of the magnesium-deficiency data derived from rat studies have been obtained with diets rich in calcium and phosphorus, although the marked imbalances in dietary Ca/Mg and P/Mg are rarely noted. Usually they provided from 600/1 to 60/1 ratios of Ca/Mg. For example, rats reported by Hess *et al.* (1959) were fed a diet delivering 18 mmol Mg/kg of diet and 150 mmol Ca; the deficient group were given 0.25 mmol Mg. They had mitochondrial swelling of tubular cells (observed as early as 3 days of magnesium deprivation) in the distal segment of the convoluted tubule and extending to the thick descending limb. By 6 days, Henle's loop was also involved. Tubular necrosis was noted by 12 to 20 days, and there were calcium deposits intracellularly and in the lumina, forming calcareous casts. The semisynthetic magnesium-deficient diet provided by Mishra (1960a,b) provided a similar Ca/Mg ratio, and caused decreased renal mitochondrial count and increased tubular calcinosis. With an approximately tenfold less disparity between dietary calcium and magnesium, tubular lesions developed in the renal cortex and at the corticomedullary junction by the day 8 of magnesium deficiency (Kashiwa, 1961). Some of the tubular cells were hypertrophied and had vacuolated cytoplasm, others were flattened, and there were numerous calcareous deposits, especially at the corticomedullary junction. Comparable changes, with clumping of renal tubular mitochondria, were correlated with functional renal defects after as little as a week of magnesium depletion (W. O. Smith *et al.*, 1962). The rats exhibited a decreased ability to concentrate and acidify urine and a marked phosphaturia.

Sauberlich and Baumann (1949) found that mice fed diets deficient in thiamine, pyridoxine, or magnesium had aminoaciduria. In a study of chicks and rats (with a Ca/Mg ratio, even in the magnesium-deficient group of rats that was less imbalanced, about 40/1; Bunce *et al.* (1963) showed that sixfold higher intakes of magnesium were necessary to prevent nephrocalcinosis and aminoaciduria that were seen in the deficient groups. Progressively increased aminoaciduria was also produced in rats on the usual high Ca/Mg dietary ratios of magnesium deficiency studies as the depletion developed (Mazzocco *et al.*, 1966).

Noted in most of the cited magnesium-deficiency studies were the intraluminal

calcareous deposits in the corticomedullary area, and the damage to the tubular epithelium. The characteristic early lesion has been described as microliths in the thin limb, the bend of the loop, and the ascending limb of the loop of Henle (ALLH) (Whang *et al.*, 1962; Welt, 1964; Oliver *et al.*, 1966; Schneeberger and Morrison, 1965, 1967; Whang *et al.*, 1969). Ko *et al.* (1962) reported that rats on a magnesium-deficient diet that provided twice as much calcium as phosphorus developed the typical intraluminal and cellular deposits of calcium phosphate, but that the ALLH was not involved unless there was phosphate loading, as well. Schneeberger and Morrison (1967) showed that the ALLH lesions of magnesium deficiency were intensified by phosphate loads. Similar intraluminal lesions have also been seen in the bend of the loop and in the ALLH of early experimental hyperparathyroidism (Epstein, 1960) and vitamin D toxicity (Epstein *et al.*, 1958; Kent *et al.*, 1958; Veltman, 1959; Potvliege, 1962). This observation is not surprising since both hyperparathyroidism and hypervitaminosis D increase blood and thus urinary loads of calcium, and cause magnesium loss.

Damage to the ALLH by primary or secondary magnesium deficiency creates a situation that intensifies the magnesium deficit. Micropuncture studies have shown that most active renal tubular reabsorption of magnesium occurs at this site (Wen *et al.*, 1970, 1971; Brunette *et al.*, 1974, 1975; Dirks and Quamme, 1978; Quamme *et al.*, 1976/1980). Thus, damage to the cells of the ALLH can cause renal tubular magnesium wasting. The clinical significance of treatment of hypomagnesemic hypocalcemia with calcemic agents or phosphates is discussed elsewhere in this volume.

13.2. Intensification of Magnesium Deficiency and Renal Damage by Excess Vitamin D (Animal)

Vitamin D toxicity, with or without high calcium intakes, has long been known to cause soft tissue damage. The cardiovascular lesions have attracted most notice. Even brain damage and calcification have been described, both in test animals and in infantile hypercalcemia (Review: Seelig, 1969b). How much of the total renal damage of most experimental magnesium-deficiency studies is caused by relative or absolute vitamin D excess, and how much might be due to excess phosphate intake or tubular reabsorption, each of which intensifies magnesium loss and increases mobilization of bone constituents has not been resolved (Fig. 13-1). The answer must await definitive studies that evaluate the effects of each agent, with the others kept at the amounts necessary to avoid inducing specific deficiencies or imbalances. Such might evoke hormonal responses that could obfuscate the effect of the mineral under investigation.

Konetzki *et al.* (1962) showed sequential accumulation of calcium and mucopolysaccharides in nephrocalcinosis due to vitamin D toxicity. The renal deposition of calcium started before the kidneys began to accumulate radioactively tagged sulfur. After the process had started the ^{35}S uptake intensified. Giacomelli *et al.* (1964) observed that calcium deposited as hydroxyapatite crystals intraluminally in the proximal convoluted renal tubules and in the cytoplasmic vacuoles of the tubular

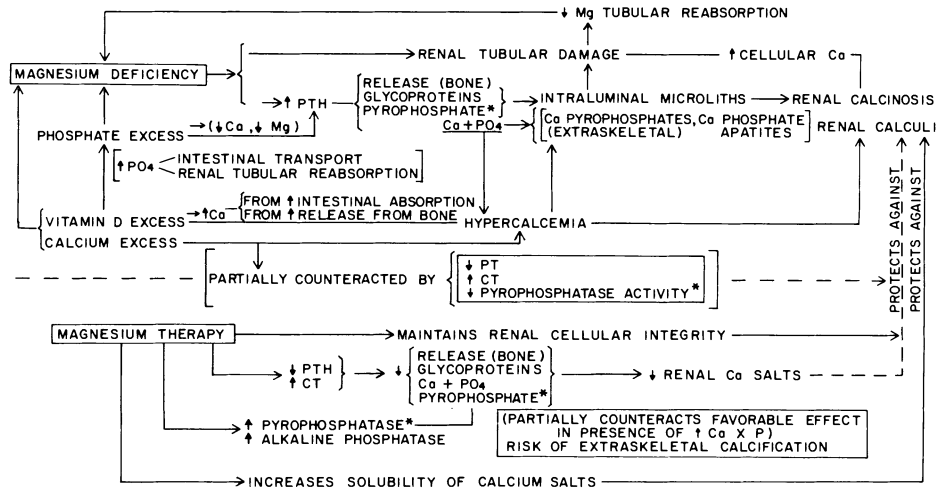

FIGURE 13-1. Interrelations involving magnesium in renal calcification processes. *Pyrophosphatase breaks down pyrophosphate (inhibitor of mineralization).

cells of rats poisoned by vitamin D. They consider the crystallization process to be induced by deposition of mucopolysaccharides (derived, like the calcium and phosphate, from the bone, dissolution of which is caused by hypervitaminosis D). These changes are very much like those described in magnesium-deficient rats: tubular calcium phosphate on a glycoprotein matrix (Bunce and Bloomer, 1972). As with that of magnesium deficiency, the initial lesion of vitamin D nephrotoxicity is proposed to be cytochemical and cytologic alterations (Scarpelli, 1966). The earliest consistent changes, by light microscopy, was increased atypical cytoplasmic vacuoles in the proximal tubular cells [manifest within 24 hours after a single massive oral dose (45,000 units) of vitamin D]. Slight mitochondrial damage was also seen. Intracellular edema and marked cellular distortion developed after four doses. Calcific deposits were first seen after six doses of vitamin D, and involved the tubules of the corticomedullary junction. At this time there was marked mitochondrial damage. There was progressive uncoupling of oxidative phosphorylation of the kidney mitochondria, a functional abnormality demonstrable also with magnesium deficiency (Vitale *et al.*, 1957b; Skou, 1962).

13.3. Intensification of Magnesium Deficiency and Renal Damage by Excess Phosphates (Animal)

Diets high in phosphate cause not only bone damage and intensify the cardiovascular lesions of magnesium deficiency but also cause renal damage and calcinosis. Shelling and Asher (1932), who were studying the intensification of vitamin D toxicity by diets high in phosphorus and low in calcium, found that even without any vitamin D supplementation, rats on high P/Ca diets developed hypocalcemia,

hyperphosphatemia, and "peppering" of the kidneys with calcium deposits, especially in the corticomedullary zone. When given moderately high vitamin D doses (400 times the antirachitic dose), the rats on high P/Ca intakes developed metastatic calcification and died rapidly, in contrast to the tolerance of much higher doses of vitamin D by rats on a 1:1 P/Ca ratio. Maynard *et al.* (1958) demonstrated that the severe organ changes of magnesium deficiency reflect imbalance among magnesium, calcium, and phosphorus. The diets that produced the highest blood levels of calcium and phosphorus and the lowest blood levels of magnesium caused the greatest renal damage and calcinosis. Forbes (1963) showed that rats fed diets high in phosphorus but low not only in magnesium but in calcium had the greatest degree of renal calcification, even more than the magnesium-deficient rats fed diets high both in calcium and phosphorus. Bunce *et al.* (1965) also demonstrated that the renal calcinosis of magnesium-deficient rats was aggravated by increasing the dietary phosphate. They also found that increasing the magnesium intake protected against renal calcification. Spaulding and Walser (1970), concerned about the use of high-dosage phosphate therapy in hypercalcemia, administered amounts of phosphate equivalent to those used clinically to rats with hypercalcemia from hypervitaminosis D. They showed that the phosphate clearly increased calcium deposition in kidneys and heart.

Calves fed a magnesium-deficient diet that was not high in calcium but that was relatively high in phosphorus had renal interstitial fibrosis, with some fibrosis of Bowman's capsule; 7 of the 21 calves had marked tubular necrosis, usually with deposits of calcium (L. A. Moore *et al.*, 1938). Comparable lesions were seen in cows with cardiovascular and articular damage associated with a conditioned magnesium deficiency (Arnold and Fincham, 1950).

The marked susceptibility of a strain of mice with hereditary diabetes to cardiac and renal calcification when fed a diet with a high phosphorus/magnesium ratio (1.2/0.04% of diet), and a phosphorus/calcium ratio of 1, for as little as 10 days (Hamuro *et al.*, 1970) is an intensification and acceleration of the changes that develop later spontaneously in this strain. The degree of calcification was little affected by lowering the calcium intake, but was reduced by increasing the magnesium intake to 0.24% of the diet. It was prevented by increasing the magnesium intake to 0.8% of the diet.

Rats with phosphate-mineralocorticoid-cardiac necrosis also have renal calcinosis, and high dosage magnesium is protective (Selye, 1958a,g).

13.4. Mediation by Secondary Hyperparathyroidism; Protection by Parathyroidectomy

The possible source of the mucoprotein that provides the matrix for calcium deposition in magnesium-deficient animals (Bunce and Bloomer, 1972; Bunce and King, 1976/1980) in bone is suggested by the work of Engel (1952). They showed that administration of parathyroid extract resulted in depolymerization of glycoprotein ground substance of bones and cartilage, and deposition of glycoprotein granules in the renal tubules. Bradford *et al.* (1962) confirmed that rats given parathy-

roid extract exhibited deposition of intraluminal glycoprotein material, which preceded calcification. Heaton and Anderson (1965) considered the renal cellular damage and calcification of their magnesium-deficient rats (which were fed a diet containing 590 mg of calcium, 440 mg of phosphorus, and 0.3 mg of magnesium/100 g to be due to secondary hyperparathyroidism, as a result of the magnesium depletion. Parathyroidectomy prevented the renal calcification caused by magnesium deficiency (Heaton and Anderson, 1965), just as it did that caused by phosphate loading (Clark and Rivera-Cordero, 1972b), which also causes nutritional hyperparathyroidism (Clark and Rivera-Cordera, 1972a; Krook *et al.*, 1975; Review: Clark, 1977). Selye (1958c) showed that PTH, in combination with NaH_2PO_4, caused intense nephrocalcinosis, as well as cardiovascular and bone damage; magnesium chloride was protective against all three experimental lesions.

13.5. Tissue Magnesium Loss and Damage: Not Parathyroid-Mediated

Exploring the mechanisms by which the phosphate-steroid-cardiorenal damage is experimentally produced, and which was first attributed to mediation by hyperparathyroidism, Lehr (1965b) found that sodium phosphate loading of parathyroidectomized rats caused cardiorenal damage even more rapidly than it did in intact rats. In fact, PTH was protective in this model (Lehr *et al.*, 1967). As his group has demonstrated for the cardiovascular system, the sodium phosphate-loading causes tissue magnesium loss and tissue damage, which precedes the rapid induction of renal calcinosis. These animals succumbed with hypocalcemic tetany, cardiorenal necrosis, and calcinosis. Thus, even though comparable lesions could be produced by calcemic agents such as vitamin D or dihydrotachysterol, in the absence of parathyroid glands, the hypercalcemia was not the cause of the lesions. As is suggested by the magnesium-deficiency studies, soft tissue calcification occurs in damaged recipient sites. Lehr *et al.* (1966, 1967) concluded that depletion of cellular magnesium, however induced, might be involved in initiation of cellular injury, necrosis of both heart and kidneys following demonstrated sharp drops in magnesium levels in both organs of parathyroidectomized sodium phosphate-loaded rats (Lehr *et al.*, 1966). This pharmacologic model is useful in demonstrating the common denominator in dissimilarly caused cardiorenal damage, cellular magnesium depletion. The nature of the lesions, and the sites at which they occur probably depend upon factors such as concomitant hypercalcemia or hyperphosphatemia, levels of local enzymes or mineralization-inhibitors, and physicochemical factors such as pH and the influence of high concentrations of the minerals involved in precipitation of calcium crystals.

13.6. Phosphatases and Extraskeletal Mineralization

Alkaline and pyrophosphatases have been found, not only in bone, where they function to increase mineralization by breaking down the pyro- and other polyphos-

phates that inhibit mineralization, but also in normal soft tissues, including the cardiovascular system, liver, brain, and kidneys (Gomori, 1941; Kabat, 1941; Kabat and Furth, 1941; Zetterström, 1951; Kirk, 1959; Kunitz and Robbins, 1966; Romanul and Bannister, 1962) and in urine (Fleisch and Bisaz, 1962b). Avioli *et al.* (1965) noted that elevated urine pyrophosphate levels characterize rapid bone turnover or breakdown, paralleling hydroxyproline outputs. This compound inhibits crystallization of calcium phosphate as apatites. Thus, an increase in its concentration in urine of patients with osteolysis sheds light on McGeown's (1969) report that the evidence of kidney stones is inversely related to that of osteoporosis.

Low levels of activity of pyro- or alkaline phosphatase should diminish the breakdown of these calcification inhibitors. The inhibition of pyrophosphatase by calcium (Kunitz and Robbins, 1966) might explain the paradoxical finding that there was less calcium deposition in kidneys of magnesium-deficient rats, loaded with phosphate and calcium, than there was in those in which the calcium intake was low (Forbes, 1963). It also helps to understand the protection against renal calcinosis of magnesium-deficient rats by calcium administration (Rayssiguier and Larvor, 1973, 1974); and the observations of Hamuro *et al.* (1970), who fed a strain of diabetic mice diets with different contents of calcium, phosphorus, and magnesium. The mice low in all these elements had more renal and cardiac calcification than did the magnesium/phosphorus-deficient mice on a normal calcium intake. Whether this reflects calcium inhibition of tissue phosphatase is speculative. In a subsequent study, in which the test mice were fed diets low in magnesium and phosphorus, but adequate in calcium, the plasma alkaline phosphatase levels fell from the high levels seen in control diabetic magnesium-supplemented mice (Hamuro, 1971). At the time the low plasma enzyme levels were obtained, there was renal and cardiac calcinosis, a surprising finding, unless the plasma levels are not indicative of the soft tissue levels. It must be noted that these diabetic mice, which have higher plasma alkaline phosphatase levels on the stock diet than do control nondiabetic mice, spontaneously develop calcinosis, although much more slowly than when they are magnesium depleted.

Manifestly, the degree of stimulation of inhibitors of alkaline or pyrophosphatase levels by high magnesium or calcium levels, respectively, cannot be the entire story. The cellular and membrane damage caused by magnesium depletion allows for an intracellular uptake of excess calcium, with deposition of calcium phosphate (usually amorphous but sometimes crystalline) in the damaged cells. Also, patients with hypercalcemia are prone to metastatic calcification despite pyrophosphatase inhibition by calcium. Formation of calcium pyrophosphate dihydrate crystals, such as have been identified in joints might negate the inhibition by pyrophosphate of calcium salt precipitation, when there is hypercalcemia.

13.7. Magnesium Effect on Precipitation of Calcium Crystals in Urine

There are complex interrelations that determine whether or not urine crystals will form in the renal parenchyma or urine. For example, urine containing pyro-

phosphate has been shown both to inhibit crystallization of calcium oxalate and hydroxyapatites of calcium phosphate (Fleisch and Bisaz, 1962a; R. G. Russel *et al.*, 1964), and to increase the formation of calcium oxalate (Review: Finlayson, 1974). Mucopolysaccharides have been shown to provide the nidus for calcium precipitation in magnesium deficiency and conditions that enhance osteolysis, and to inhibit aggregation and growth of calcium oxalate crystals (W. G. Robertson *et al.*, 1973). Another inconsistency is the hypercalcemia produced by hypervitaminosis D or hyperparathyroidism, which usually is not associated with urolithiasis. Kushner (1956) noted that both conditions cause increased citrate levels, and concluded that citrate-complexing of urinary calcium functions to prevent urolithiasis. There are many other factors that influence susceptibility to stone formation. Only data directly referable to magnesium are considered, briefly, here.

It has long been known that increased concentration of magnesium in the urine increases the solubility of calcium oxalate (Hammarsten, 1929). Rats fed magnesium-deficient diets, which were rich in oxalates and which produced an alkaline urine, had a high incidence of renal calcification and bladder stones; providing a balanced diet without a high Ca/Mg ratio both prevented stone formation and solubilized some that had been formed (Hammarsten, 1938). Mukai and Howard (1963) showed that addition of magnesium to urine of stone-forming patients blocked the ability of such urine to induce mineralization of collagen *in vitro*. Administration of about 100 mg of magnesium (as the oxide) three times daily, to 11 patients, with recurrent calcium oxalate crystalluria and stone formation, eliminated the crystal formation, although the oxalate was still being excreted, to a lesser degree. The investigators surmised that the magnesium interfered with formation of the crystals. C. Moore and Bunce (1964) found that administration of 420 mg of magnesium oxide daily prevented idiopathic hypercalciuria and stone formation and passage in two subjects within two weeks of starting the treatment. One had formed calcium oxalate stones and one had formed calcium phosphate stones. One had the magnesium therapy discontinued after freedom from calculi for five months, and again began passing stones within two weeks. Prien (1965), on the basis of Gershoff's (1959) work indicating the role of pyridoxine deficiency in oxalate formation, included supplementation with 10 mg of pyridoxine hydrochloride with 4 tablets of magnesium hydroxide (providing about 400 mg Mg/day) in his treatment of calcium oxalate stone-formers. Most of his series of 50 patients showed a marked reduction in formation of new stones. Gershoff and Prien (1967) discussed the mechanisms that might be involved in the increased solubility of the calcium salt excreted, the oxalate of which was only moderately reduced, and the calcium of which was actually increased by 25% in patients treated for a year. Of 36 patients who were observed on treatment for 5 years, 30 had no recurrence or decreased incidence of stone formation. They consider the possibility that increased urinary citrate of magnesium-treated patients (that had been low in the stone formers) might be contributory to the increased solubility of calcium. Melnick *et al.* (1971/1973; 1971) have reported similarly favorable results among 95 recurrent calcium oxalate stone formers treated with 100 mg of magnesium as the oxide twice daily for two years, and among 47 treated for 4 years. J. Thomas *et al.* (1978) have demonstrated *in vitro* and *in vivo* that magnesium inhibits formation of calcium oxalate crystals. They have obtained the best clinical results with use of magnesium trisilicate, providing

300 mg of magnesium daily. It may be this simple physicochemical effect that is responsible for the difference in incidence of urolithiasis in hard- and soft-water areas (pp. 21–24).

13.8. Clinical Renal Diseases Possibly Related to Magnesium Deficiency

The experimental evidence that magnesium deficiency during pregnancy produces greater fetal than maternal magnesium deficiency raises the possibility that renal tubular abnormalities, such as are produced in weanling magnesium-deficient animals, might occur *in utero*. No studies of the renal structure of fetuses of experimental magnesium-deficient mothers have been found, and thus this possibility remains speculative. Microscopic examination of kidneys of stillborn babies of mothers subject to magnesium deficiency should provide valuable data.

After birth, there are several conditions that lead to magnesium deficiency, both in the neonatal period and later in infancy. Infants who do not survive neonatal asphyxia or sodium bicarbonate or sodium lactate treatment of their neonatal or postoperative acidosis, both anoxia and acidosis causing egress of magnesium from the cells, should have their renal parenchyma carefully studied, especially for evidence of tubular cellular and subcellular damage. The kidneys of erythroblastotic infants failing to survive exchange transfusion with citrated blood (which chelates magnesium) should be similarly examined. Definitive data can be obtained from experimental models of these perinatal abnormalities, which can provide electron microscopic evidence of very early renal changes, as well as light microscopic evidence of sequellae. Such studies should include evaluation, not only of kidneys, but of cardiovascular tissues (especially intramural coronary arteries, myocardium, and endocardium) and bone.

Because neonatal hypocalcemia is usually noted first, and usually aggressively treated with calcemic agents to control the neuromuscular irritability and convulsions, what might be an underlying magnesium deficiency is usually detected only by the time magnesium depletion has developed to the point of severe hypomagnesemia. Familial magnesium malabsorption might be a contributory factor in infants and children with the most severe manifestations. Neonatal magnesium deficiency and hypoparathyroidism secondary to gestational magnesium deficiency in some instances, and to high phosphate + vitamin D intakes in others, is likely to contribute to less severe but possibly damaging tissue magnesium loss. The renal damage of such treatment might lead to long-term intensification of magnesium deficiency by causing damage to the portion of the renal tubules where active magnesium reabsorption occurs.

13.8.1. Renal Tubular Defects in Magnesium Reabsorption

As noted earlier, most active renal tubular reabsorption of magnesium occurs in the ascending limb of the loop of Henle (ALLH), which provides insight into clinical magnesium wastage, most early experimental magnesium deficient renal

damage occurring in the tubular cells of the corticomedullary area, with microliths of the loop of Henle, convoluted and distal tubules, and with damage to ALLH. That these experimental findings are relevant to the clinical situation is suggested by fragmentary findings.

Whether magnesium deficiency contributes to clinical aminoaciduria, as it does in the experimental model should be investigated. Its occurrence in renal tubular acidosis, vitamin-D-resistant rickets, and hyperreactivity to vitamin D, in all of which conditions magnesium deficiency might play a role, is suggestive.

13.8.1.1. Contributions to Clinical Renal Magnesium Wastage by Calcemic Factors and Phosphate Therapy

Calcium deposits in the lumens of the proximal renal tubules and of the ALLH have been described in an infant whose symptomatic hypocalcemia had been unsuccessfully treated with calcium infusions and high-dosage vitamin D, before severe magnesium deficiency was detected in a specimen taken the last day of life (Vainsel *et al.*, 1970). Another infant, whose persistent infantile hypocalcemia had been treated by intensive calcium therapy and then, when complicated by intractable diarrhea, with addition of high-dosage vitamin D (10,000 U/day) was then found to have hypomagnesemia and tubular acidosis. At autopsy there were calcium deposits in the distal tubules and collecting ducts. No parathyroid tissue was found at autopsy (Taitz *et al.*, 1966). Infants with hypervitaminosis D and infantile hypercalcemia, which seems to be caused by hyperreactivity to vitamin D (Review: Seelig, 1969b) have also been found to have intraluminal calcium deposits predominantly in the outer half of the renal medulla (Dawson *et al.*, 1954; Rhaney and Mitchell, 1956). Nephrocalcinosis infantum, that Lightwood (1935) first associated with renal tubular acidosis, hypophosphatasia, hyperoxalemia, and sarcoidosis (which is associated with hyperreactivity to vitamin D) is also associated with renal tubular lesions and calcium deposits involving Henle's loop and tubules immediately proximal and distal to it (J. A. James, 1956; Kushner, 1956; Shanks and MacDonald, 1959; T. Ferris *et al.*, 1961; Paunier *et al.*, 1968a). Hyperreactivity to vitamin D, of infants who were receiving excessively fortified milk and infant foods was implicated in Great Britain in renal tubular acidosis (Fig. 13-2) (Lightwood and Butler, 1963) and in nephrocalcinosis (Shanks and MacDonald, 1959). Development of such abnormalities in children who were being given high-dosage vitamin D for vitamin D-refractory rickets (with or without aminoaciduria) or for idiopathic hypoparathyroidism and hypocalcemia (T. Ferris *et al.*, 1961; Paunier *et al.*, 1968a; Moncrieff and Chance, 1969) suggests that magnesium deficiency might have played a contributory role, first to the vitamin-D-refractory rickets or hypocalcemia and then to the increased susceptibility to nephrotoxicity of vitamin D. It seems plausible that the presenting tetany and convulsions of the babies with hypocalcemia, renal tubular acidosis, and nephrocalcinosis (J. James, 1956; Ferris *et al.*, 1961) might have been contributed to by magnesium deficiency. Familial renal tubular wasting of magnesium has been reported in siblings with renal tubular acidosis, renal calcinosis, and hypocalcemia that was resistant to very high doses of vitamin D (Michelis *et al.*, 1972). The older child (a 10-year-old girl) had active rickets; the

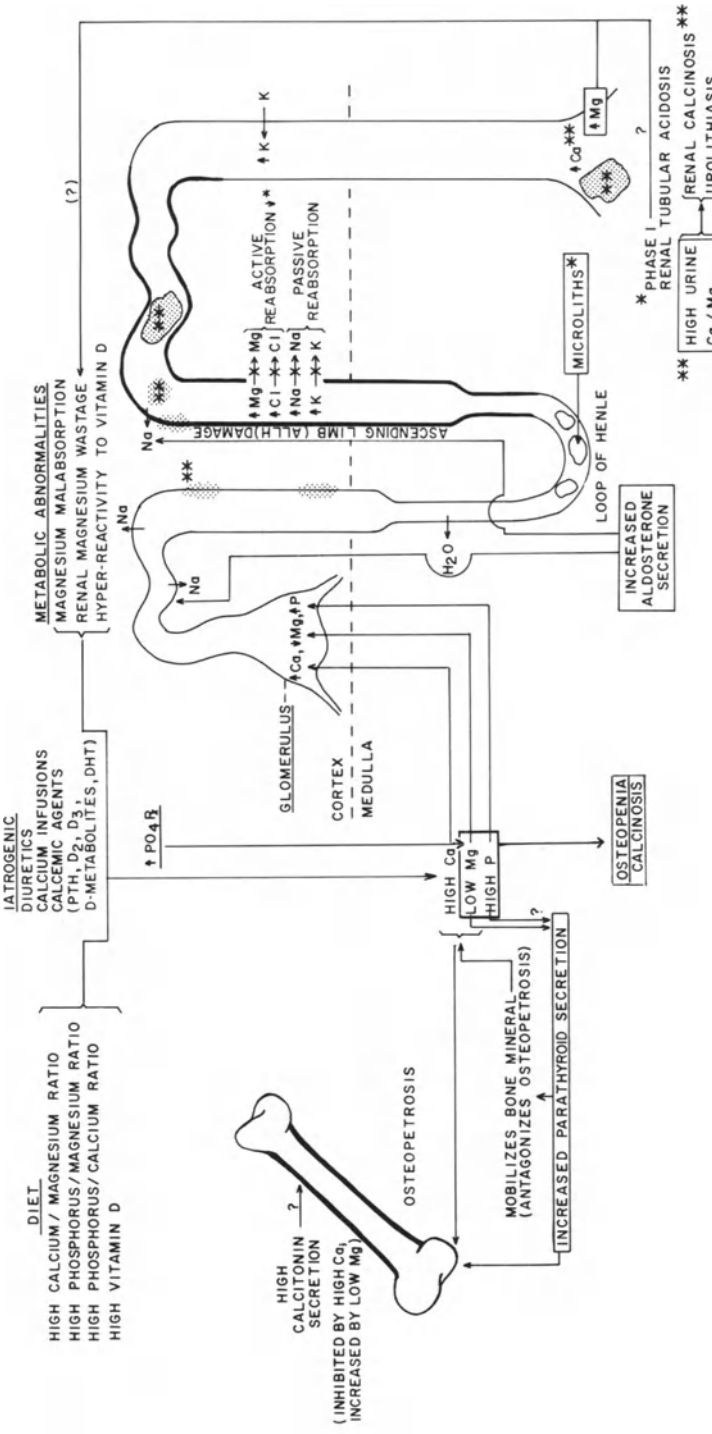

FIGURE 13-2 Magnesium deficiency with hypercalcemia: Skeletal and renal consequences.

bone age of the younger brother (6 years old) was three standard deviations below normal. Neither child's hypomagnesemia (1.1, 1.2 mEq/liter) responded to high-dosage oral magnesium supplementation, a failure found due to renal wastage rather than malabsorption of magnesium. It is conceivable that the initiating abnormality in these children might have been hyperreactivity to vitamin D, which might have led to hypercalcemia and ALLH damage, that was responsible for their persistent renal magnesium wastage. It is provocative, however, that both children had been born prematurely. The older child was jaundiced at birth and developed a convulsive disorder at the age of 6. The younger child underwent surgery at 6 weeks of age. The premature births and complicated neonatal courses might have contributed to early magnesium deficiency that might have contributed to hyperreactivity to (toxic effects of) vitamin D. The older child had had polyuria from the age of two; the younger child from the age of 1.

Another child with vitamin-D-resistant rickets was found to have hypomagnesemia (0.7 mEq/liter) and two times the normal renal clearance of magnesium when he was ten years old, following two years of very high (15 mg/day) vitamin D dosage (Sann *et al.*, 1975). He had manifestations similar to those seen in infantile hypercalcemia during the first year of life (anorexia and insomnia), and he exhibited poor growth. He had clear evidence of kidney disease from two years of age, at which time he developed proteinuria; by six he had polyuria and polydipsia and marginally high serum calcium. By eight he had skeletal demineralization, for which the high-dosage vitamin D was prescribed. Renal biopsy showed juxta-glomerular hyperplasia, and he had hyperrenism and normotensive aldosteronism. At this time, sodium restriction caused hyponatremia. Angiotensin-infusion did not raise his blood pressure, and he was judged to have a form of Bartter's syndrome (Bartter, 1962). A second renal biopsy confirmed the juxta-glomerular hyperplasia and revealed proliferative endarteritis of the efferent arterioles. Two years later, the osteoporosis had progressed, and his phosphaturia, magnesiuria, and hypophosphatemia and hypomagnesemia were identified and found to be refractory to the potassium-sparing diuretic (triamterene) that was given in the hope that it might spare magnesium. It is provocative that hypomagnesemia has also been identified in Bartter's syndrome (Brackett *et al.*, 1968; Sutherland *et al.*, 1970; Mace *et al.*, 1973), a condition that Kurtzman and Gutierrez (1975) suggest may be a syndrome caused by ALLH dysfunction.

Reviews of the literature on renal damage caused by hypercalcemia-inducing agents such as vitamin D excess (Epstein, 1960) and hyperparathyroidism (Pyrah *et al.*, 1966) show that the earliest lesions are in the loop of Henle, the ALLH, and the distal convoluted tubules and collecting tubules and that the duration of the hypercalcemia can be as short as one to three days to produce significant damage. The damage becomes irreversible with sustained hypercalcemia. That such lesions can cause renal magnesium loss is suggested by the work of Massry *et al.* (1967), who reported an acquired defect in renal tubular reabsorption of magnesium in a 44-year-old woman with surgical hypoparathyroidism. They considered the renal defect as one likely to have been caused by hypercalcemia, subsequent to long-term treatment with vitamin D and thiazide diuretics (each of which favors retention of calcium over magnesium). Hypomagnesemia was detected (0.9–1.2 mEq/liter), which was not corrected by withdrawal of the diuretic and the vitamin D. Her high renal

clearance of magnesium persisted, and did not change on administration of PTH. Hypercalcemia of immobilization of an adolescent boy, who had suffered multiple fractures, also resulted in sustained increased renal clearance of magnesium (Hyman *et al.*, 1972).

It is possible that early renal tubular damage, caused by calcemic agents *(supra vide)* or by phosphate therapy that causes soft tissue calcinosis, including renal tubular damage (Bulger *et al.*, 1930; Albright *et al.*, 1932; Carey *et al.*, 1968; Marti and Cox, 1970; Dudley and Blackburn, 1970) can be reversed with adequate magnesium repletion, once the hypercalcemia has been controlled. A clue that this may be so derives from the observations of Dooling and Stern (1967), who studied the magnesium status of a six-day-old infant whose hypocalcemic convulsions had been intensively treated with oral and parenteral calcium. (It should be kept in mind that such infants are also generally hyperphosphatemic. The baby excreted large amounts of magnesium (16.3 mg/kg/24 hr) while he was hypomagnesemic (0.6–0.7 mEq/liter) and being treated by intramuscular administration of 0.25 ml of 50% magnesium sulfate every 6 hours (25 mEq Mg^{2+}/24 hr). His urinary magnesium output did not fall until the magnesium dosage was doubled. By the fourth day of high-dosage magnesium, with resultant stable elevation of his serum magnesium level at 1.6 mEq/liter, his urinary magnesium output had fallen to 3.06 mg/kg/24 hr, a five-fold drop in daily urinary magnesium output. It is tempting to speculate that microliths might have formed in the loops of Henle, with resultant early damage to the broad ascending limb when he was being loaded with calcium and was magnesium depleted. Early during the magnesium supplementation, there might have been impaired tubular reabsorption of magnesium. When the amount of magnesium given was increased, solubilization of presumed calcium microliths and tubular cells might have taken place, with resultant increased active tubular reabsorption of magnesium.

13.8.1.2. Contribution to Clinical Renal Magnesium Wastage by Malabsorption

Specific genetic magnesium malabsorption or general intestinal malabsorption might cause severe enough magnesium depletion to cause renal tubular damage directly, or as a consequence of calcemic therapy of secondary hypocalcemia. Direct evidence that this might be so has recently been provided by Rapado and his colleagues (Rapado *et al.*, 1975; Rapado and Castrillo, 1976/1980a). They reported a 12-year-old child with a diagnosis of nephrocalcinosis from early life, who developed overt rickets when her hypercalciuria was treated, first with sodium cellulose phosphate and then with hydrochlorthiazide. She was then found to have hypomagnesemia (0.5 mEq/liter) and required parenteral magnesium therapy because she was both a magnesium malabsorber and renal waster. Of two additional patients with nephrocalcinosis, one young man with latent tetany of hypomagnesemia (0.75 mEq/liter) and hypocalciuria (6.8 mg/100 ml), reported by this group, was a renal magnesium waster. Their third patient with hypomagnesemic (0.65 mEq/liter) nephrocalcinosis was a young man whose urinary magnesium levels did not decrease on a low-magnesium intake, and whose fecal excretion of magnesium was

higher than his intake, suggesting magnesium malabsorption. This patient's serum calcium level was only marginally low (8.3 mg/100 ml), and he had tachycardia and hypertension. All three patients had hypercalciuria, and their urinary calcium output increased with magnesium therapy.

The patient reported by Freeman and Pearson (1966) as a renal tubular waster of magnesium, had had a history suggestive of steatorrhea and growth failure during her first year of life, which suggested early magnesium depletion. She came from a family with a high incidence of hypomagnesemia: One of her sons had serum magnesium levels of 1.12, 1.20 mEq/liter on two occasions; another son, a sister, a maternal cousin, a daughter, and the patient's mother had marginally low serum Mg levels (1.50, 1.47, 1.68, 1.51, and 1.70 mEq/liter, respectively, strongly suggestive of a genetic trait. Whether the inherited trait was primary renal dysfunction or magnesium malabsorption is not clear. Another patient, one who had had gastrointestinal disease (ascariasis, followed by gastroenteritis) before she was two years old, exhibited subsequent growth failure, intermittent glycosuria and aminoaciduria, and X-rays suggestive of osteoporosis (B. Booth and Johanson, 1974). The boy, whose hypomagnesemia was not detected until he was six years of age (Miller, 1944), might have had infantile hypomagnesemia, as suggested by his long history of neuromuscular irritability. His osteochondritis of three years duration, resembling that of a five-year-old boy with renal magnesium wasting (Klingberg, 1970), suggested to Booth and Johanson (1974) that the child reported by J. F. Miller (1944) might also have had a renal tubular defect. It should be noted, however, that the defect might as readily have been in intestinal absorption of magnesium.

Perhaps the first recorded instances of excessive urinary output of magnesium despite marked hypomagnesemia were two patients with peptic ulcers, one with prolonged nasogastric suction (who undoubtedly was not absorbing normal amounts of magnesium) and another who had had several complicated surgical procedures (Martin *et al.*, 1952). That surgical patients do not conserve magnesium efficiently during the early postoperative days has been shown repeatedly. Data are generally not available on the nature of the antacids taken, prior to the suction or surgery, but if they were calcium rather than magnesium preparations, the patients might have had a relatively high Ca/Mg dietary ratio prior to the acute situation that intensified their magnesium loss.

Note should be taken of the incomplete distal renal tubular acidosis seen in two women who developed hypomagnesemic hypocalcemia as a result of intestinal malabsorption: one following intestinal resection for regional enteritis, the other with nontropical sprue (Passer, 1976). Since these patients had hyperparathyroidism (by immunoassay) and treatment with magnesium alone corrected the abnormal renal function, the author speculated that the resistance to the calcemic effects of the endogenous PTH might be related to abnormalities in vitamin D metabolism, which was corrected by the magnesium.

13.8.1.3. Miscellaneous Factors in Renal Magnesium Wastage

Randall *et al.* (1959) was the first to propose a functional renal tubular defect as an explanation for the failure of a 38-year-old man with mild diabetes mellitus,

pyelonephritis, focal seizures, and electrocardiographic abnormalities to conserve magnesium. Before dying with extensive arteriosclerosis and myocardial infarct, he had exhibited hypokalemic alkalosis, hypocalcemia, and hypophosphatemia. They noted that additional patients with renal tubular disease wasted magnesium. Two adult sisters and an unrelated 22-year-old woman were first identified as having impaired renal conservation of magnesium and potassium, in association with metabolic alkalosis; one also had hypochloremia (Gitelman *et al.*, 1966a). The sisters had dermatologic manifestations resembling those seen in magnesium-deficient animals; the third patient had recurrent carpopedal spasm. All exhibited slightly elevated aldosterone secretion without hypertension and had minor ECG abnormalities; two had muscle weakness.

Chronic hypomagnesemia and recurrent episodes of neuromuscular irritability and severe abdominal pain have recently been attributed to a renal tubular defect in magnesium reabsorption in a boy, whose mother also has had subnormal serum Mg levels (Paunier and Sizonenko, 1976/1980). As in the previously reported patients with this renal defect, even supplementation with large doses of magnesium failed to normalize the serum magnesium levels.

The oldest patient, at the time of first detection of renal wastage of magnesium, is a postmenopausal woman who developed normocalcemic latent tetany of marginal deficiency several years after total hysterectomy (Seelig *et al.*, 1975). She has a less severe form of renal Mg wasting and less marked hypomagnesemia than the other cited patients. Her condition is associated with normotensive, intermittent aldosteronism and increased plasma renin activity (PRA), only manifest in response to dietary Mg restriction or to hormonal challenge (i.e., deoxycorticosterone acetate) that increased her magnesium deficit (Seelig *et al.*, 1976/80). Since she has also had hypochloremia, it has been proposed that she has malfunction of the ALLH, where not only magnesium but chloride is actively reabsorbed (Rocha and Kokko, 1973; Burg and Green, 1973; Kurtzman and Gutierrez, 1975). It seems plausible that her renal dysfunction and concomitant abnormalities—sodium retention, peripheral edema, hypokalemia responsive to magnesium, hypercapneic alkalosis, and hormonal aberrations—may be the result of magnesium insufficiency, since all of these findings have been reported in experimental magnesium deficiency (Review: Seelig *et al.*, 1976/1980; Whang and Welt, 1963; Ginn *et al.*, 1967; Cantin, 1970; Elin *et al.*, 1971a; El Shahawy, 1971; Cantin and Huet, 1973).

13.8.2. Renal Damage during Pregnancy: Related to Magnesium Deficiency?

Magnesium deficiency has been implicated in preeclampsia and eclampsia. Possibly it contributes to the renal damage of eclampsia. The involvement of the small (coronary) arteries in magnesium deficiency makes one suspicious that the renal arteriolar disease of young toxemic primiparas (Smythe *et al.*, 1964), who are particularly prone to magnesium deficiency of pregnancy, might also be a consequence of magnesium inadequacy. DeAlvarez and Gabrio (1953) implicated arteriolar spasm in the decreased glomerular filtration rate of patients with toxemias of pregnancy.

The attempts to counter the leg cramps of pregnancy (which might be contributed to by magnesium deficiency) by calcemic therapy, might intensify the magnesium deficiency directly and as a result of damage to renal tubular cells *(supra vide)*. The resultant high calcium/magnesium ratio particularly in arterial tissue [such as has been implicated in increased arterial tension (Review: Haddy and Seelig, 1976/1980)] might similarly be a factor in the hypertension of abnormal pregnancy. Calcemic supplements to magnesium-deficient pregnant women might contribute to urinary calculi of pregnancy, which has reported in 0.05–0.35% of pregnancies. (McVann, 1964; R. Harris and Dunnihoo, 1967). Since estrogen lowers the urinary content of calcium and raises its citrate level (Shorr, 1945), both effects that militate against calcium stone formation, the degree of magnesium deficiency might well be fairly profound for calcareous stones to form during pregnancy. On the other hand, the resultant hyperparathyroidism of pregnancy might directly increase the propensity toward renal calcinosis formation, as well as hypertension, both being consequences of hyperparathyroidism (Review: Pyrah *et al.*, 1966).

13.8.3. Diabetic Renal Disease: Contributed to by Magnesium Deficiency?

Only brief reference will be made here to the speculation that magnesium deficiency might be contributory to proliferative arteriolar sclerosis, found in the kidneys as well as in other tissues, including the myocardium. As in experimental magnesium deficiency, in which there is arteriolar disease with subendothelial, muscle wall, and endothelial proliferation, with increased wall thickness/lumen ratio, renal (and other) arterioles have subintimal and medial abnormalities with encroachment on the lumen (Review: Ditzel, 1954). The lesions are not identical pathologically and the glomerular capillary changes of the Kimmelstiel-Wilson lesion have not been described in magnesium deficiency, but loss of magnesium by diabetic patients raises the possibility that the arterial changes might have a component contributed to by magnesium deficiency.

14
Intensification of Magnesium Deficiency by Calcemic and Phosphate Therapy

The possibility that magnesium deficiency might be contributory to, or might accompany, the abnormalities that cause ostopenia, hypocalcemia, hypercalcemia, and renal and cardiovascular disease is rarely considered in initiating therapy. Refractoriness to direct attempts to correct hypocalcemia and hypokalemia are now increasingly leading to investigation of serum magnesium levels, and less frequently to other (better) means of ascertaining the body's magnesium status. Emphasis is placed, in this chapter, on the problems that can result from treatment of either hypo- or hypercalcemia by agents that cause magnesium loss, when the primary disorder is one resulting in magnesium deficiency. Accepting the difficulties in evaluating the magnesium status, it is proposed that serum magnesium levels and 24-hour urinary magnesium outputs be made part of the routine initial diagnostic program. Since higher serum levels of magnesium are tolerable without serious hazard, except perhaps when there is hypercalcemia, it is suggested that magnesium therapy be tried before calcium loading of patients who have disorders that might make them susceptible to magnesium deficiency.

14.1. Calcemic Therapy during Pregnancy

It is usually recommended that pregnant women drink ample amounts of milk (which in most industrialized countries is "fortified" with antirachitic amounts of vitamin D) and take vitamin supplements that also provide an antirachitic dose of vitamin D. As pointed out earlier, the magnesium intake is likely to be meager. Then, when leg cramps of pregnancy develop (which can be caused by magnesium deficiency and hypomagnesemic hypocalcemia), the usual therapeutic approach is generally administration of calcium. Rarely is the magnesium status investigated,

and magnesium treatment tried. There have been publications, however, that have shown that, both in normal and abnormal pregnancy, serum levels of magnesium tend to be low, even when corrected for hemodilution. Metabolic balance studies have shown that normal pregnant women should ingest sufficient magnesium to maintain a strongly positive balance, to meet both her needs and those of the fetus. It has been proposed that some of the abnormalities of pregnancy might be a consequence of magnesium deficiency. The fetus might be at even greater risk, experimental gestational magnesium deprivation causing greater fetal than maternal magnesium deficiency. Factors that increase magnesium requirements, such as gestational hypervitaminosis D, have caused congenital cardiovascular, renal, and skeletal defects. Suggestive evidence has been presented, and a theory promulgated that magnesium deficiency during pregnancy might be contributory to several "congenital" abnormalities of the heart, arteries, kidneys, and bones. Cardiac outflow abnormalities (such as can be produced by experimental hypervitaminosis D) have been found in conjunction with endocardial fibroelastosis. Infantile coronary or generalized arteriosclerosis, cardiomyopathy, and dysrhythmias, sometimes leading to sudden death, are seen alone or in combination with gross cardiac abnormalities. Such infants often have renal calcinosis, and if they survive the early months often have growth and mental retardation. Osteogenesis imperfecta, which resembles lesions that have been produced in pups of vitamin-D-poisoned rats, also resembles lesions of severe congenital hypophosphatasia, and is sometimes accompanied by cardiac and renal abnormalities, such as are seen in hypervitaminosis D. Neonatal hypoparathyroidism is common, and must be attributable to influences *in utero,* speculated to be gestational magnesium deficiency. One may wonder whether more intense magnesium depletion might so suppress the parathyroids *in utero* as to be responsible for congenitally deficient parathyroid tissue: "idiopathic" primary hypoparathyroidism. When the diseases are severe or familial, the patient's and the mother's intestinal absorption and renal tubular reabsorption of magnesium should be explored, as should that of other close relatives; since familial defects of magnesium metabolism have been recognized, it is conceivable that this might be a flaw that intensifies lesions caused by other heritable disorders, or even underlies some of them.

There is a wide spread of vitamin D requirements and susceptibility to its toxicity. Thus, the practice of routinely providing much more than prophylactic amounts of vitamin D during pregnancy should be reevaluated, taking into account the usually high dietary intakes of phosphate, which, like low-magnesium intakes, intensifies vitamin D toxicity. Requiring investigation is the influence of such imbalances on the maternal organism and the placenta, and systematic investigation of the fetal organs and bones should be undertaken of stillborn infants, and of experimental models. Until definitive experimental data are available, we should keep in mind that magnesium has protected against experimental vitamin D and phosphate toxicity, and that magnesium deficiency (as is likely during pregnancy, especially in immature mothers and in women who have had frequent pregnancies, but also in less stressed mothers) has intensified the lesions of hypervitaminosis D and phosphate loads. Thus, magnesium supplementation (to a total of at least 7–10 mg/kg/day) is suggested as a minimum for those without magnesium malabsorption or

renal wastage. If either of those abnormalities of magnesium metabolism is detected (and it should be sought if there is a familial history of suspect abnormalities), the magnesium supplementation should be correspondingly higher, and might have to be parenterally given.

14.2. Calcemic Therapy during Infancy

Considered in detail are the risks of treating neonatal hypocalcemia, which might well be a consequence of magnesium depletion, with calcemic agents. Failure of response of neuromuscular irritability is often the first clue to the necessity of evaluating the magnesium status, and favorable response to magnesium therapy the proof. However, during the time that a magnesium-deficient infant is being loaded with calcium, or given agents that cause bone resorption, damage can be inflicted on the heart, arteries, kidneys, and bones, and (especially in babies with genetic susceptibility to abnormalities of these tissues) permanent lesions might result. For example, magnesium deficiency and vitamin D excess each causes lipid abnormalities and damage to small and large arteries, respectively. In addition, the early renal lesions of magnesium deficiency (in the face of calcemic factors) are in the tubules, in the area of active magnesium reabsorption. Thus, such therapy might be contributory to establishment of transitory or permanent renal magnesium wasting. With continued calcemic treatment (or dietary custom that provides only moderate excess of vitamin D to infants who are hyperreactive to vitamin D, are magnesium deficient, or both), cardiac outflow abnormalities, endocardial fibroelastosis, premature atherosclerosis, renal calcinosis, and osteosclerosis, as well as mental retardation, might result.

14.3. Calcemic Therapy for Osteopenias

The use of high-dosage vitamin D or its derivatives in the treatment of refractory osteopenias might similarly result in cardiovascular and renal damage, other soft tissue calcinosis, and osteosclerosis, rather than normal bone, which requires optimal magnesium for normal osteocyte activity and matrix formation. Little has yet been done to correlate the osteopenia or brittle chalky bones produced by either experimental magnesium deficiency or by vitamin D excess, the degree depending on the amount of calcium and phosphate in the diet. As regards the use of high-dosage calcemic agents for postmenopausal osteoporosis, reference should be made to the estrogen/parathyroid/magnesium interrelationships that suggest that magnesium's effect on osteocytes and matrix formation might find applicability in preventing further loss, if not serving to increase formation of organic matrix.

Inadvertent proof was provided that hypervitaminosis D produces metastatic calcification when very high doses of vitamin D were used to treat arthritis, even when the intake of calcium was not high (Danowski *et al.*, 1945; Mulligan, 1947; Frost *et al.*, 1947; Howard and Meyer, 1948; Reed, 1950; Christensen *et al.*, 1951; Verner *et al.*, 1958). In such instances, the calcium, phosphate, and matrix were

drawn from the skeleton and deposited in soft tissues. In one of the studies (Frost *et al.*, 1947) magnesium was studied and found to be low during the vitamin-D-toxic period and to rise when the overdosage was stopped. The evidence that some arthritic processes might be consequences of magnesium depletion suggests that seeking and correcting magnesium deficiency might be useful.

It is advisable to explore the magnesium status of patients with osteopenias before loading them with calcemic agents, which might prove useless in some or unduly toxic in others if magnesium deficiency is present. If hypercalcemia has already been induced by high doses of such agents as vitamin D or its congeners or metabolites, or by parenteral loads of calcium, the magnesium serum level and 24-hour urinary output should be determined. A parenteral magnesium load may be inadvisable until the hypercalcemia is corrected, and not by phosphate loading.

14.4. Treatment for Hypercalcemia

Because hypercalcemic crises are life-threatening, emergency treatment is directed toward lowering the circulating calcium levels quickly, by hydration with saline or dextrose in water, and increasing its urinary excretion with a potent diuretic such as furosemide, by administration of phosphate to increase its precipitation, hopefully in the bones, and by agents such as calcitonin to shift the calcium to bone, or mithramycin to antagonize bone resorption (Newmark and Himathongkam, 1974). Corticosteroids, which act more slowly, are recommended in long-term control of chronic hypercalcemia. Unfortunately, saline and furosemide diuresis, phosphate loads, and corticosteroids all increase magnesium loss, which is also caused by the hypercalcemia as well as frequently by the diseases that caused the hypercalcemia in the first place. Furthermore, inorganic phosphates have resulted in ectopic, sometimes fatal calcification *(infra vide)*.

Hydration and furosemide diuresis are acceptable, until calcitonin can be obtained. Calcitonin is a preferable agent because it increases deposition of calcium in bone, stimulating bone alkaline pyrophosphatase (Orimo *et al.*, 1970), without transferring calcium to soft tissue sites (Chausmer *et al.*, 1965). In fact, there have even been reports that calcitonin protects against soft tissue calcification (Gudmundsson *et al.*, 1966; Kenny and Heiskell, 1965; Gabbiani *et al.*, 1968; Rasmussen and Tenenhouse, 1967; Rayssiguier and Larvor, 1974a). Once the plasma calcium levels are lowered, magnesium therapy can be substituted for the calcitonin, evidence having been obtained that calcitonin secretion is stimulated by increased magnesium (Radde *et al.*, 1970; Bell and Kimble, 1970; Care *et al.*, 1971; Littledike, 1970; Littledike and Arnaud, 1971; S. P. Nielsen, 1974). Additionally, moderately increased magnesium levels suppress parathyroid secretion (Care *et al.*, 1966; Buckle *et al.*, 1968; Gitelman *et al.*, 1968a; Massry *et al.*, 1970b; Sherwood, 1970; Sherwood *et al.*, 1970; Altenahr and Leonhardt, 1972). Competition between calcium and magnesium for a common renal tubular reabsorptive pathway (Samiy *et al.*, 1960a,b; Charbon and Hoekstra, 1962; Ardill *et al.*, 1962; Heaton *et al.*, 1964; Massry and Coburn, 1973) has also been credited for the increased urinary excretion of calcium and drops in serum calcium that accompany magnesium loads

(Womersley, 1956; Chesley and Tepper, 1958; Kelly *et al.*, 1960; Kemeny *et al.*, 1961; S. P. Nielsen, 1970; Nielsen and Jorgensen, 1972).

It is recommended that magnesium not be given until the acute hypercalcemia has been lowered, intensification of soft-tissue calcinosis having been produced by magnesium, given to rats with experimental hypercalcemia caused by hypervitaminosis D (Whittier and Freeman, 1971).

14.4.1. Risks of Phosphate Therapy

Inorganic phosphate therapy has been utilized and warned against for many years in the treatment of hypercalcemia and of skeletorenal disorders. Oral administration of inorganic phosphates was found, almost 50 years ago, to reduce the acute hypercalcemia of patients with hyperparathyroidism (Bulger *et al.*, 1930; Albright *et al.*, 1932). However, both groups of investigators expressed concern about the risk of promoting nephrolithiasis or other extraskeletal calcification. Bulger *et al.* (1930), for example, found extensive calcification of lungs, gastric mucosa, and kidneys when a patient died of bronchopneumonia a few days after the infusion. Shortly thereafter, Bulger and Gausman (1933) demonstrated that hyperparathyroidism causes negative magnesium balance. In 1962, Dent reintroduced phosphate therapy for hypercalcemia. One of his patients responded well; the other developed extensive painful ectopic calcification. Four years later, R. S. Goldsmith and Ingbar (1966) again described the usefulness of phosphate loads for the treatment of life-threatening hypercalcemia, applying it also to patients with neoplasms. They obtained rapid and dramatic decreases of serum calcium levels and improvement of symptoms in 16 of their 20 patients. Ten died, of whom 7 had autopsies. Five had extraskeletal calcification. One, who had not been examined postmortem, had died of a massive infarction the day after the phosphate infusion. Because of uncertainty that these six instances were related to the treatment, and because of the rapidity with which the phosphate lowered the plasma calcium level, R. S. Goldsmith (1970) reiterated his recommendation that this approach was most valuable for hypercalcemic crisis in his critical review of Eisenberg's (1970) caution as to the risk of producing metastatic calcification. Eisenberg (1970) noted the instances in which such calcification had been reported after either intravenous or oral administration of large doses of phosphates, and warned of the likelihood that the calcium would precipitate out in soft tissues. For example, Schackney and Hasson (1967) reported hypotension and acute renal failure in two patients whose hypercalcemia had been treated by phosphate infusions. One had extensive metastatic calcification in the heart, lungs, kidneys, and pancreas; the other exhibited no metastatic calcification on autopsy. Breuer and LeBauer (1967) reported a patient with multiple myeloma and hypercalcemia, who had a good temporary clinical and chemical response to intravenous and oral phosphate treatment, but who suddenly died with renal insufficiency and pneumonia and was found to have extensive pulmonary and renal calcification. Carey *et al.* (1968) reported metastatic calcification involving the endocardium, coronary arteries, and kidneys (glomerular, intraluminal, and interstitial) in a patient whose hypercalcemia of neoplastic origin had been treated with inorganic phosphate infusions. Marti and Cox (1970) reported addi-

tional patients who developed irreversible calcinosis, particularly of renal tubules and lungs, following phosphate infusions for hypercalcemia resulting from bone metastases. Dudley and Blackburn (1970) recommended slit lamp conjunctival examination to detect early extraskeletal calcification, such as they found in seven of nine patients who had been treated with high-dosage oral phosphates. Five had been treated for hypercalcemia; two with hyperparathyroidism developed impaired renal function during therapy. Of four normocalcemic patients, who were being given phosphate therapy for renal calculi, three developed conjunctival calcification, one developed radiologic evidence of renal and one of arterial calcification.

Thus, although inorganic phosphate has been effective in reducing hypercalcemia and the incidence of calcific urinary stones, it carries the risk of soft-tissue calcinosis, such as is seen with magnesium deficiency, and is intensified by phosphate loading. Monsaingeon *et al.* (1971/1973) found that oral inorganic phosphate loads (2.25 g/day) decreased the urinary magnesium concentration more than it did that of calcium in 70% of 29 patients with urinary calculi. They cautioned that it is necessary to monitor magnesium levels in patients treated with phosphates.

Short-term administration of cellulose phosphate to normal subjects has reduced the intestinal absorption and urinary output of both calcium and magnesium (Dent *et al.*, 1964), and caused a gradual decline in serum magnesium (but not calcium) levels (Parfitt, 1975). That long-term administration of cellulose phosphate, given to reduce the urinary calcium in stone formers, can cause magnesium depletion is indicated by Sutton's (1968) study. He reported hypomagnesiuria and hypomagnesemia in a recurrent stone former, who had been treated with a low calcium diet and oral cellulose phosphate for 6 years. His plasma magnesium remained between 0.65 and 1.25 mEq/liter and his 24-hour urinary magnesium between 2 and 15 mg during a year of observation, while he was on that regimen.

Other phosphates have induced fewer problems, possibly in part because of lesser depletion of magnesium, and in part because of their increase in urinary output of inhibitors of calcium crystallization in urine. For example, orthophosphate (disodium hydrogen phosphate dihydrate) administration (12 g/day = 1.98 g P/day) to patients with recurrent renal calculi, to reduce the intestinal absorption of calcium and thereby to reduce urinary calcium excretion, was found also to increase the urine citrate and pyrophosphate levels, but to influence the magnesium levels and balance only slightly. It caused a more profoundly negative calcium balance, decreased urinary calcium output, but caused a net increase in the Ca/Mg urinary ratio. The crystallizing propensity was reduced, probably largely because of the orthophosphate-induced pyrophosphate and citrate levels. The investigators who showed that inorganic pyrophosphate inhibits the precipitation of hydroxyapatite crystals *in vitro* (Fleisch and Neuman, 1961) developed condensed phosphates (diphosphonates) that are less readily hydrolyzed and that are effective in preventing ectopic calcification *in vivo* (Irving *et al.*, 1966; Francis *et al.*, 1969). A diphosphonate, which is under investigation for its inhibition of ectopic calcification and of bone resorption (Francis *et al.*, 1969; Fleisch *et al.*, 1969; Russell *et al.*, 1971; Michael *et al.*, 1971; Saville and Heaney, 1972), has been shown to cause negative magnesium balance on long-term in children with ectopic calcification (Uttley *et al.*, 1975).

With so much evidence that magnesium deficiency accompanies hypercalcemia and its treatment, it is tempting to recommend prompt magnesium repletion. However, one must keep in mind the magnesium dependence of phosphatases that destroy the polyphosphates (including the pyrophosphates) that inhibit precipitation of calcium salts in the soft tissues. In fact, several of the British investigators, who reported the severe form of infantile hypercalcemia, suspected that use of magnesium laxatives might have intensified the syndrome that is characterized by renal, cardiovascular, and brain damage and calcinosis. Thus, as indicated earlier, serum calcium levels should be lowered first, by the least dangerous means, before instituting magnesium therapy. Without hypercalcemia or hyperphosphatemia, magnesium activation of soft-tissue alkaline or pyrophosphatase should not present a danger of precipitation of calcium phosphate salts. Magnesium stimulation of bone alkaline or pyrophosphatase should function to take up calcium and phosphate, particularly if the magnesium suppresses parathyroid and increases calcitonin secretion.

14.5. Complex of Diseases to Which Magnesium Deficiency Contributes, Especially When Complicated by Calcemic and Phosphate Therapy

Among the tissues damaged by magnesium deficiency, those of the cardiovascular and skeletal and the urinary tract are listed on Table 14-1. Some of the abnormalities cited in several of the diseases to which there is reason to believe magnesium deficiency is contributory are disorders that are comparable to those seen in experimental magnesium deficiency. Unfortunately, some of the early findings (such as hypocalcemia, neuromuscular irritability, and osteopenias) suggest direct treatment with the obviously deficient substance, calcium, or by agents that normally function to increase calcium absorption and its blood levels. When the hypocalcemia or osteopenia is secondary to magnesium depletion, such treatment can intensify the magnesium loss, increase the cellular damage (caused by magnesium deficiency), and lead to metastatic calcinosis (Figure 14-1).

Thus, the underlying abnormality (metabolic or dietary or both) that prevents normal magnesium utilization can lead to abnormal function or response to parathyroid hormone, vitamin D, or calcitonin, with possible production of a variety of osteopenias. Most of the diseases have their roots during gestation or early infancy. One, postmenopausal osteoporosis, is entered because of the possibility that the drop in estrogen secretion might contribute to relative hyperparathyroidism. High dietary phosphate intakes, which can contribute to major disorders of infancy, might also play a significant role in the high incidence of osteoporosis and periodontosis later in life. This can be intensified in the treatment of life-threatening hypercalcemia of malignant disease and hyperparathyroidism.

The use, not only of phosphate therapy (which has a distinct risk of metastatic calcinosis), but of high-dosage calcemic agents during infancy (to counter hypocalcemia and refractory osteopenias), and to treat postmenopausal, senile, or disuse

TABLE 14-1. Abnormalities Encountered in Infantile Disorders and Seen with Magnesium Deficiency

Abnormality	Disorder[a]
Cardiovascular	
Arteriosclerosis	LBW; ↓, ↑ Ca Inf.; SID; IHD Inf.; OI; D-RR; N-I; G,MR; Mg Malabsorpt.; Ren. Mg Wast.; ↑-React. D
Cardiomyopathy (Necrosis, cell infiltration, fibrosis, calcinosis)	LBW; ↓, ↑ Ca Inf.; SID; IHD Inf.; OI; D-RR; N-I; RTA; G,MR ↓ Pasia; Ren. Mg Wast. C-F
Conduction system abnormality	LBW, ↓, ↑ Ca Inf.; SID: OI; ↓ Pasia; RTA; Mg Malabsorpt.
Outflow obstruction (valve, major arteries)	↑ Ca; SID; OI; ↓ Pasia, D-RR; ↑ React.-D; G,MR; C-F
Endocardial fibroelastosis	LBW; SID; IHD Inf.; RTA; ↑ React.-D; Mg Malabsorpt., Wast.
Hypertension	↑ Ca; D-RR; ↑ React.-D; Mg Malabsorpt., Wast.
Hyperlipemia	↑ Ca; ↑ React.-D; D-RR
Skeletal/Articular/Dental	
Osteopenia	LBW, ↓ Ca; ↓ Pasia; RTA; OI; D-RR; Mg Malabsorpt.
Osteosclerosis	↑ Ca; ↑ React.-D; Dyschondr.; IHD; G,MR
Spontaneous fractures	LBW; OI; ↓ Pasia; Dyschondr.
Articular abnormality	↑ Ca; OI; ↓ Pasia; Dyschondr.
Dental abnormality	↑ Ca; ↑-React.D; OI; ↓ Pasia
Renal	
Renal tubular damage	
Mitochondrial, cellular calcinosis	LBW: ↑ Ca; D-RR; ↑ React. D; Arrhythm.; IHD; SID; Ren Mg Wast.
Intraluminal: Glycoprotein	LBW; D-RR; ↑ Ca; OI; Dyschondr; Arrhythm.; IHD; Ren. Mg Wast.
Intraluminal: Calcium (microliths)	
Aminoaciduria	OI; ↑ Ca; D-RR; Dyschondr.; A.S.; Ren. Mg Wast.
Calcareous urolithiasis	↑ Ca; A.S.

[a]Abbreviations: Arrhythm.: arrhythmia; A.S.: arteriosclerosis; ↑, ↓ Ca: hypo-, hypercalcemia; C-F: cardiofacies; ↑ D React.: hyperreactivity to vitamin D; D-RR: vitamin-D-resistant rickets; Dyschondr.: Dyschondroplasia; GR: growth retardation; Inf: infantile; IHD: ischemic heart disease; LBW: low birth weight; MR: mental retardation; N-I: nephrocalcinosis infantum; OI: osteogenesis imperfecta; ↓ Pasia: hypophosphatasia; Ren. Mg Wast.: renal magnesium wastage (1° or 2°); RTA: renal tubular acidosis; SID: sudden infant death.

osteoporosis, also intensifies magnesium loss and metastatic calcification. Such treatment also increases bone mineralization, but in the absence of optimal magnesium, the bone has abnormal matrix. Such treatment is likely to cause increased bone density, but decreased bone elasticity, with resultant marblelike, brittle bones. Renal dysfunctions—tubular acidosis, aminoaciduria, and calcinosis and calculi—might also result from magnesium deficiency, intensified by calcemic therapy.

This book presents evidence that early investigation of the magnesium status is important. Whether use of magnesium supplements during gestation and infancy will reduce the incidence of some of the indicated congenital anomalies will require many years to ascertain. Clues might be obtained from experimental models, prepared so as to mimic some of the nutritional imbalances, and to exaggerate magne-

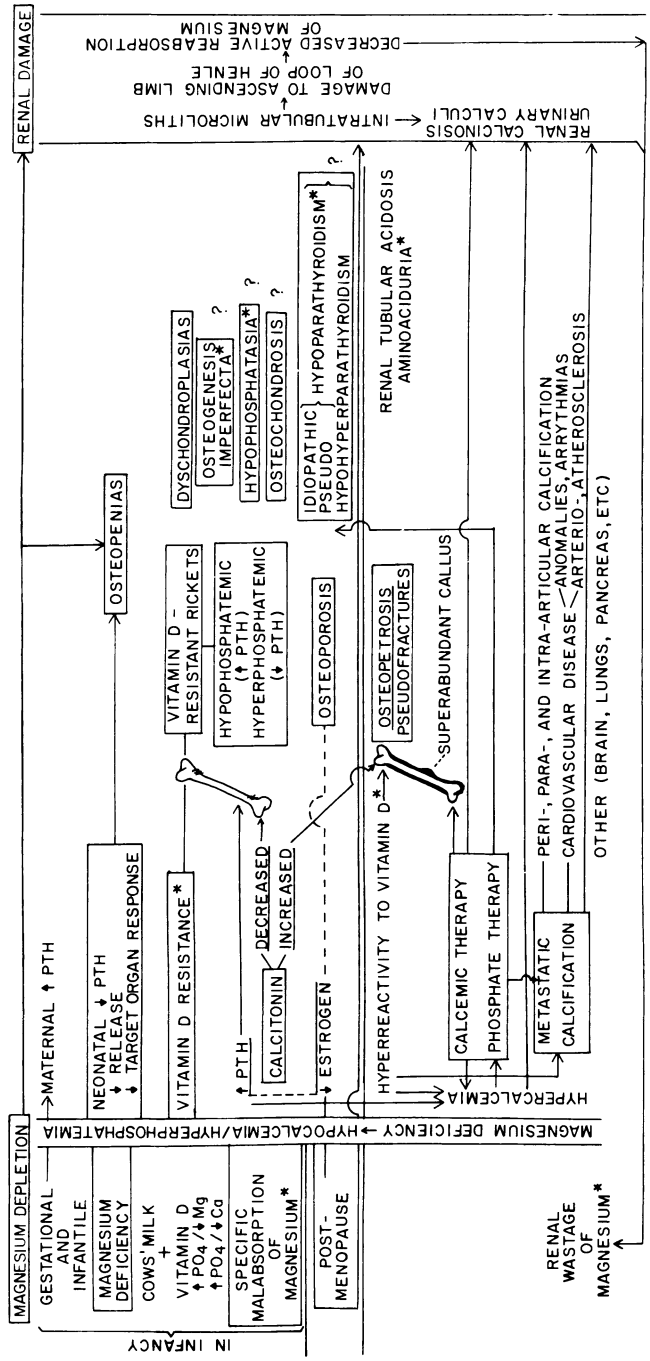

FIGURE 14-1. Magnesium deficiency in pathogenesis of diseases: skeletal, renal, and cardiovascular.

sium deficiency, such as might be found with genetic magnesium malabsorption or renal wastage. Since magnesium administration is benign (unless there is renal failure), it is proposed that prophylactic and therapeutic trials are justifiable.

This particularly true for patients with premature cardiovascular disease, or for subjects with familial histories suggesting high risk of early ischemic heart disease or strokes. It is also true for patients with the bone disorders cited, and for those with functional renal disorders such as tubular acidosis and aminoaciduria, and for patients with calcific urinary tract disease.

Appendix
Tests for Magnesium Deficiency
Cases of Infantile Ischemic Heart Disease

There are serious problems in assessing the magnesium status of patients, probably the most important reason that, despite the ubiquity of this element and its importance in so many enzyme systems and in function and structure of vital organs and bones, magnesium is usually one of the last clinical parameters to be explored (Whang *et al.*, 1976/1980). When levels are sought, the results are often misleading. Each means of evaluation has its limitations, and in order to determine whether a patient is magnesium deficient (unless the deficiency is so profound as to cause unquestioned hypomagnesemia), a combination of approaches may be necessary. First of all, although magnesium is an intracellular cation, second in concentration only to potassium [the retention of which is dependent on magnesium-dependent enzymes (Reviews: Wacker and Vallee, 1958; Whang *et al.*, 1967; Whang, 1968, 1971; Seelig, 1972; Whang and Aikawa, 1977)], serum magnesium is generally the only parameter explored. Unfortunately, the reliability of serum magnesium values is dubious as an index of body levels, and even as an indication of abnormal blood levels, particularly when wide ranges of serum or plasma magnesium levels are accepted as "within normal limits" *(infra vide)*.

With the limitations of serum magnesium values, the clinician must rely on indirect tests of magnesium metabolism, determinations of cellular magnesium levels (e.g., blood cells, skeletal muscle) generally being unattainable and not standardized *(infra vide)*. Metabolic balance studies have provided important baseline data regarding magnesium requirements of normal subjects (Seelig, 1964). However, metabolic research units are necessary to obtain reliable results and the procedure is time consuming and cumbersome. Furthermore, when used with patients who have intrinsic (isolated, possibly familial) magnesium malabsorption, or who have renal magnesium wastage as a result of renal disease or a genetic trait, the results can be misleading. Prolonged studies, and periods of magnesium restriction (which might be of risk to patients with underlying magnesium deficiency) would be necessary to separate those who do not retain magnesium because their tissue stores are ample from those who have a metabolic abnormality resulting in magnesium malabsorption or renal wastage. Also, such studies are inapplicable to patients

who require medication that can interfere with the intestinal absorption or renal tubular reabsorption of magnesium.

At this time, the most reliable method of evaluating a patient's magnesium status is determination of its 24-hour urinary output before and after a parenteral magnesium load, and evaluating the percentage retention in terms of renal function and serum magnesium levels *(infra vide)*.

A.1. Limitations of Serum or Plasma Magnesium Levels

A.1.1. What is the Normal Range?

Serum magnesium levels are normally maintained within a very narrow range, with a coefficient of variation of only 10% to 20% (Alcock *et al.*, 1960; Hanna, 1961b; Prasad *et al.*, 1961; Stewart *et al.*, 1963; Ginn, 1968; Hunt, 1969; Henrotte and Durlach, 1971; Rousselet and Durlach, 1971; Seelig and Berger, 1974), unless there is a profound deficiency, or magnesium load in the face of renal failure. Thus, the serum or plasma magnesium level is not a reliable index of magnesium deficiency (Walser, 1967; Gitelman and Welt, 1969; Henrotte and Durlach, 1971; Rousselet and Durlach, 1971). To make matters worse, there are many sources of error even in the most reliable technic available, atomic absorption spectrophotometry (Table A-1). Thus, each laboratory should establish its own mean and narrow range of normal values (Hunt, 1969; Seelig and Berger, 1974). Not acceptable as "within normal limits" are values that fall between 1.5 and 2.5 mEq/liter, a wide range obtained from data reported from many laboratories, and that has been designated as the normal "reference" range (Unsigned, *N Engl J Med,* 1974) (Table A-2).

TABLE A-1. Sources of Error in Magnesium Determinations

Delay in separation of plasma, serum, hemolysis →↑ Serum, plasma Mg[a]	
Deproteinization by different methods	
Plasma vs. serum re { clotting of plasma / sedimentation of protein }	Loss of Mg[a–c]
Trichloracetic acid →↓ values[d]	
Wet ashing: Interference by sulfate[e]	
Dry ashing: Adherence to porcelain[d]	
Loss by spattering	
Differences in analytic methods	
Storage of dilute specimens →↓ values[d]	
Chemical interference by presence of calcium, strontium, and sulfate	

[a]Stephan and Speich (1972).
[b]Welin and Speich (1973).
[c]Cummings, NA, *et al.* (1968).
[d]Hunt, BJ (1969).
[e]Stewart, WK, *et al.* (1963).

TABLE A-2A. Magnesium Serum Values (mEq/liter) Reported as Normal

Procedure	Investigators and year	Number of subjects in study[a]	Range	Mean
Molybdivanate precipitation	Simonson *et al.* (1947)	21	1.58–2.07	1.72
	Stutzman and Amatuzio (1953)	17		1.82 ± 0.2
	Smith and Hammarsten (1958)	40	1.14–1.82	1.48 ± 0.17
	Thoren (1963)	90	1.43–1.93	1.68 ± 0.125
Titan yellow	Heagy and Burton (1948)	10		1.89 ± 0.015
Accuracy stated unreliable	Orange and Rhein (1951)	45	1.58–2.07	1.89
because of interfering	Baldwin *et al.* (1952)	?	1.7 –2.2	
substances in biological material	Albert *et al.* (1958)	43	1.36–1.94	1.61 ± 0.14
	Graham *et al.* (1960)	7	1.83–2.44	2.15 ± 0.20
	Barker (1960)	64		1.82 ± 0.37
	Prasad *et al.* (1961)	?		1.81 ± 0.13
	Durlach (1969a)	64		1.98 ± 0.13
EDTA, eriochrome black-T	Smith (1955)	24	1.75–2.50	2.1 ± 0.2
	Carr and Frank (1956)	20	1.60–1.96	1.72 ± 0.08
	Kim *et al.* (1961)	?		1.60 ± 0.20
	Walser (1961)	20	1.68–2.08	1.92 ± 0.12
	Wallach *et al.* (1962)	77	1.75–2.34	2.0 ± 0.15
	Opie *et al.* (1964)	?	1.5 –1.75	
With semiautomatic or	Sones *et al.* (1960)	?	1.7 –2.0	1.8 ± 0.07
automatic equipment	Jones and McGuckin (1964)	40		1.98 ± 0.11
	McPherson (1965)	100		1.90 ± 0.2
		227		1.80 ± 0.2
	Gitelman *et al.* (1966b)	25	1.45–1.87	1.66 ± 0.11
Fluorometric	Schachter (1961)	14		1.80 ± 0.26
	Batsakis *et al.* (1964)	113	0.80–2.80	1.88 ± 0.40
	Teh (1968)	21		1.90 ± 0.036
Flame spectrophotometry	Wacker and Vallee *et al.* (1957)	14	1.85–2.56	2.05 ± 0.18
	(1960)	30	1.60–2.40	2.10 ± 0.16
	Teloh (1958)	25		2.04 ± 0.14
	MacIntyre *et al.* (1960, 1967)	76	1.50–1.80	1.66 ± 0.01
	Hanna (1961)	12	1.50–1.90	
	Montgomery (1961)	46	1.35–2.05	1.70
	Fawcett and Wynn (1961)	10		1.74 ± 0.07
	Hughes and Tonks (1965)	36	1.92–2.41	2.3
Atomic absorption spectrometry	Stewart *et al.* (1963)	60 M		1.74 ± 0.11
		40 F		1.75 ± .12
	Heaton *et al.* (1963) (1967)	?	1.43–1.90	
	Lim *et al.* (1964)	87	1.30–1.90	1.67 ± 0.14
	Hunt (1969)	14 F		1.80 ± 0.08[b]
	Henrotte (1971/1973)	46 M		1.64 ± 0.10
		182 F		1.59 ± 0.12
	Ross *et al.* (1976/1980)	19 M	1.52–2.02	1.71 ± 0.14[b]

[a]M = males: F = females.
[b]Plasma separated from cells in 30 minutes.

TABLE A-2B. Serum Magnesium (mEq/liter): Infancy and Childhood

Procedure	Investigators	Age	Number of determinations	Total Mg	% Ultrafilterable Mg
Titan yellow	Silverman and Gardner (1954)	3 mo–12 yr	43	1.77 ± 0.02	1.16 ± 0.02
Flame spectrophotometry	Anast (1964)	1–5 days	238	1.92 ± 0.27	
	Hüther (1964)	1–14 yr	98	1.80 ± 0.26	
	Kobayashi (1967)	0–5 days	13	1.64 ± 0.19	
		6–10 days	9	1.53 ± 0.15	
		11–30 days	16	1.68 ± 0.16	
		31–60 days	6	1.78 ± 0.17	
		2 mo–11 mo	23	2.26 ± 0.15	
		1–5 11/12 yr	40	2.25 ± 0.16	
		6–15 11/12 yr	15	2.16 ± 0.17	
Fluorometric	Teh (1968)	At birth	18	1.53 ± 0.05	1.05 ± 0.04
		First week	20	1.35 ± 0.05	0.88 ± 0.04
		2–4 weeks	13	1.54 ± 0.09	1.03 ± 0.08
		2 mo–1 yr	12	1.64 ± 1.07	1.08 ± 0.06
		2 yr–10 yr	13	1.68 ± 0.66	1.17 ± 0.05
		(Young adults)	21	(1.90 ± 0.04)	1.26 ± 0.02
Ultramicroscopic method (Mann dye)	Bajpai *et al.* (1966)	First week	56	1.51 ± 0.12 (1.20 ± 1.80)	
Atomic absorption spectrometry	Tsang and Oh (1970)	First 4 days	91 infants	1.54 ± 1.93	
		AGA[a]	38 infants	1.76 ± 0.03	
		SGA[b]	53 infants	1.60 ± 0.03	

[a] AGA = Average for gestational age.
[b] SGA = Small for gestational age.

A.1.2. Bound and Free Magnesium in Plasma

Rarely are efforts made to differentiate among ionized, complexed, or protein-bound fractions of serum magnesium, since expensive equipment is required for measurement of the protein-bound and diffusible fractions (Silverman *et al.*, 1954; Prasad *et al.*, 1961; Walser, 1967; S. P. Nielsen, 1969; Cummings *et al.*, 1968; Voskian *et al.*, 1973). There are no readily available means of measuring ionized magnesium. Because many factors influence the degree of binding, complexing, or chelating of magnesium, the total content of magnesium in the serum is not simply related to the availability of magnesium, either extra- or intracellularly. For example, experimental dietary magnesium deficiency has caused an increase in the protein-bound fraction (Hoobler *et al.*, 1937; Morris and O'Dell, 1969) or decreased total and ultrafiltrable fraction (Woodward and Reed, 1969). Clinical magnesium deficiency of intestinal malabsorption (Silverman and Gardner, 1954) and of hepatic cirrhosis (Prasad *et al.*, 1961) is associated with decreased protein-bound magne-

sium, and increased ultrafiltrable fraction. Possibly, the thyroid hormone affects the degree of protein-binding of magnesium (Soffer *et al.*, 1941; Dine and Lavietes, 1942; Silverman *et al.*, 1954; Prasad *et al.*, 1961), but there is no accord as to the degree or the mechanism. The level of plasma citrate, which complexes part of the ultrafiltrable fraction of magnesium, is influenced by growth hormone (Hanna *et al.*, 1961), adrenocorticosteroid hormone (Walser *et al.*, 1963), estrogen (N. F. Goldsmith *et al.*, 1970) and vitamin D (Carlsson and Hollunger, 1954). Not all of the magnesium-complexing or chelating anions in the body are known. Magnesium complexes comprise 14% of the total plasma magnesium: Mg citrate, 4%; magnesium HPO_4, 3%; unidentified complexes, 6% (Walser, 1961).

Furthermore, even the way the blood is drawn can affect the serum or plasma magnesium values. Levels are lower in serum from blood obtained quickly after applying the tourniquet than after prolonged venous stasis (Whang and Wagner, 1964, 1966; S. P. Nielsen, 1969). This may be referable to the egress of cellular magnesium in hypoxic states (Engel and Elin, 1970; Hochrein, 1966; Hochrein *et al.*, 1967). In addition, dehydration or acidosis can yield spuriously high serum magnesium levels.

A.2. The Importance of Cellular Magnesium Determinations

Until it is feasible to demonstrate cellular magnesium deficiency in a tissue that has metabolic characteristics and magnesium exchangeability, similar to that of the metabolically active tissues, conclusions as to the importance of magnesium in physiologic processes will remain open to dispute. Enzymatic studies of magnesium-dependent enzyme systems are important in providing clues as to the effects of suboptimal magnesium concentrations in the body, cells, and cell-fractions (Reviews: Wacker and Vallee, 1964; Walser, 1967; Wacker and Parisi, 1968; Heaton, 1978). Direct determinations of cellular magnesium levels, however, are necessary for clinical evaluation of the changing magnesium status of individuals under the influence of diseases and treatment regimens that alter magnesium retention.

A.2.1. Erythrocyte Magnesium

Tissue magnesium levels have most frequently been estimated on the basis of analysis of erythrocytes for magnesium. Despite investigations for over 40 years, erythrocyte magnesium levels have not proven a reliable source of information as to the clinical magnesium status. Analyses of findings from over 20 studies indicate that the means of RBC-Mg are between 1.9–3.1 mmol/liter (1.8–6.2 mEq/liter) (Review: Henrotte and Durlach, 1971). The ranges, given as normal in individual studies, are often even wider (Table A-3). Such broad "normal" ranges make it difficult to detect significiant changes in abnormal conditions.

Many procedures have been utilized in the effort to minimize sources of error,

TABLE A-3. Erythrocyte Magnesium Determinations

Investigator(s)	Indirect methods[a]		Direct methods	
	(mg/100 ml)	(mEq/liter)	Erythrocyte column	Aliquot
Greenberg *et al.* (1933)	5.4 – 7.8 6.6 ± 0.53	(5.5)		
Hald and Eisenman (1937)		3.5–6.2 (4.6 ± 0.5)		
Carubelli *et al.* (1958)		4.69–5.86 (5.29 ± 0.34)		
Wallach *et al.* (1962)		4.2–7.9 (5.6 ± 1.1)	4.3–6.4 mEq/liter (5.3 ± 0.5)	
Bruyn *et al.* (1965)		4.69–6.70 (5.53)		
Valberg *et al.* (1965)				35–75 μg/g (57 ± 8.4)
Rosner and Gorfien (1968)				36.3–64.4 μg/10^{10} rbc (49.7 ± 7.8)
Lim *et al.* (1969a)	4.4 – 8 (6.3 ± 0.98)	(5.6)		
Hellerstein *et al.* (1970)			(4.34 ± 0.54) mEq/kg rbc	
Paschen *et al.* (1971)		4.5–5.4 (5.02 ± 0.24)		
Thin (1971)				3.61–5.61 mg/g rbc (4.47 ± 0.41)
Rousselet and Durlach (1971)		(4.6 ± 0.49)		
Henrotte (1971)	M: 5.7 ± 0.59 F: 5.4 ± 0.64			
Pesquies (1971)		(4.91±0.04)		
De Elizalde (1971)		4.6–6.0 (5.3)		
Vidal Freyre and Flichman (1971)		4.5–5.0		
Drenick and Brickman (1971/1973)		3.2 – 7.1		
Stephan and Speich (1972)				45.4–65.5 mg/100 ml (52.7 ± 0.7)
Hunt and Bélanger (1972)		4.32–4.88 (4.57 ± 0.16)		
Welin and Speich (1973)				40.0–61.2 mg/100 ml (51.10)
Frazer *et al.* (1972)		3.70–4.13		
Stewart and Fleming (1973)		(5.55 ± 0.56)		

[a]Plasma Mg minus whole blood Mg, corrected for hematocrit.

and to obtain uniformity of results. The first controlled study (Greenberg *et. al.*, 1933) showed that direct measurement of the magnesium content of saline-washed erythrocytes, and indirect measurement (subtracting plasma magnesium from whole blood magnesium, and correcting for differences in hematocrits) yielded comparable results. Washing erythrocytes with isotonic saline (Greenberg *et al.*, 1933) or with buffer (Valberg *et al.*, 1965) did not cause loss of cellular magnesium. Attempts to improve validity of magnesium analysis of packed erythrocytes have included: (1) correction for trapped plasma and for differences in hemoglobin (Val-

berg *et al.*, 1965; S. Hellerstein *et al.*, 1970); (2) use of cation-exchange resins to remove all Mg from cell fragments and hemolystates (Hunt and Manery, 1970; Frazer *et al.*, 1972), (3) rapid separation cells and protein precipitates to prevent elution of magnesium into the hemolysate (Stephan and Speich, 1972; Welin and Speich, 1973); (4) saponification of unwashed erythrocytes without deproteinization (Rousselet and Durlach, 1971); (5) measurement of magnesium in washed and ashed cells, in terms of mg/g cells (Paschen *et al.*, 1971), and (6) of weight per cell count (Valberg *et al.*, 1965; Rosner and Gorfein, 1968).

Except for those who measure magnesium in ashed erythrocytes, and those using cation exchange resin on cell ghosts and hemolysates (Hunt and Manery, 1970; Paschen *et al.*, 1971), the levels are determined in hemolysates, the cell ghosts being discarded with the rest of the precipitated protein. Most of the erythrocyte magnesium is in the hemoglobin, in association with the organic phosphates and enzymes, and is released when the cells are disrupted (Rose, 1968; Bunn *et al.*, 1971). A portion of the erythrocyte magnesium, however, is bound to the membranes (Carvalho *et al.*, 1963), and remains even after repeated washing (Fujii *et al.*, 1973; Sato and Fujii, 1974). Although only 2–6% of the total erythrocyte magnesium is present in the membranes, which are separated from washed erythrocytes (Fujii *et al.*, 1973), the hemolysis procedure may provide a source of error, particularly if the disrupted cell membranes remain in contact with the hemolysate for different lengths of time. Divalent cations (Mg^{2+}, Ca^{2+}) in the suspending medium are readily bound to the disrupted membranes, both internal and external surfaces of which are exposed to the medium (Sato and Fujii, 1974). Large and variable amounts of the cations are taken up by the stroma.

The significantly higher magnesium levels in reticulocytes and young erythrocytes than in old erythrocytes (Henriques and Orskov, 1939; Bang and Orskov, 1939; Dahl, 1950; Ginsberg *et al.*, 1962; R. Bernstein, 1959) are probably responsible for the major discrepancies in reported normal erythrocyte levels. In experimentally induced reticulocytosis, the erythrocyte magnesium was 28.4 mEq/liter (in rabbits with 85% reticulocytes), in contrast to 7.8 mEq/liter in control rabbit-erythrocyte (Ginsberg *et al.*, 1962). Patients with high reticulocyte counts have higher erythrocyte magnesium levels than do those with low reticulocyte counts (Dahl, 1950; Ginsberg *et al.*, 1962: R. Bernstein, 1959). For example, a patient with 89.7% reticulocytes had RBC Mg of 4.0–4.7 mEq/liter (Ginsberg *et al.*, 1962). Because reticulocytes and young erythrocytes remain at the top of the centrifuged column of red cells, and the older erythrocytes sediment to the bottom (Keitel, 1955; R. Bernstein, 1959; Ginsberg *et al.*, 1962), when erythrocytes are analyzed for magnesium, either the entire column should be studied (S. Hellerstein *et al.*, 1960) to minimize the risk of obtaining aliquots from different levels, or only the lowest level, where the old erythrocytes are found, should be analyzed (Ross *et al.*, 1976/1980).

It is possible that marginal abnormalities in magnesium levels might be masked by procedures that measure only the hemolysate magnesium, even when the membranes are immediately separated from the hemolysate. In a study of RBC magnesium of anemic children (S. Hellerstein *et al.*, 1970), their erythrocytes had signifi-

cantly higher-than-control magnesium, in terms of Mg/cell solids, but not in terms of Mg/numbers of cells or of cell water. In a study of erythrocytes from convalescent cardiac patients (Borun, 1963) the older erythrocytes (from the botton of the centrifuged column of cells) had higher magnesium levels than did the young erythrocytes, in terms of Mg/L cell water, but not by dry weight. Whether use of agents that cause magnesium loss contribute to decreased magnesium levels in reticulocytes formed [e.g., during magnesium loss of active treatment of congestive heart failure (Wacker and Vallee, 1958; Seller *et al.*, 1966; Wacker and Parisi, 1968; Seelig, 1972; Lim and Jacob, 1972b)] seems plausible. There is direct evidence that erythrocyte-magnesium levels are significantly below normal in patients with congestive heart failure (Seller *et al.*, 1966; Lim and Jacob, 1972b).

The erythrocyte membrane instability (and tendency toward hemolysis) that is found in magnesium deficiency (Larvor *et al.*, 1965; Erlandson and Wehman, 1966; LaCelle and Weed, 1969; Cohlan *et al.*, 1970; Oken *et al.*, 1971; Battifora, 1971; Elin *et al.*, 1971b; Elin, 1973; Piomelli *et al.*, 1973; Elin, 1976/1980) may provide another source of error when erythrocyte magnesium is obtained by analysis of the hemolysate. With progressive magnesium deficiency, associated with low intra- and extracellular magnesium levels, there is increased fragility of the erythrocytes and shortening of survival time (Elin, 1973). One may speculate that the defective erythrocyte membranes may have defective binding of magnesium, thereby releasing more during laboratory-hemolysis. Whether this might yield spuriously higher erythrocyte magnesium values in hemolysates, thereby masking cellular deficiency, remains to be investigated.

Still another limitation of erythrocyte magnesium is its unreliability, as an index of magnesium status at the time of the analysis. There is poor correlation between plasma and erythrocyte levels (Wallach *et al.*, 1962; Valberg *et al.*, 1965; Hellerstein *et al.*, 1970; Ross *et al.*, 1976/1980), although in chronic conditions, such as long-term magnesium deficiency, malnutrition, chronic liver disease, and hypothyroidism, there may be low plasma and erythrocyte magnesium levels. Acute two- to fourfold increases in plasma magnesium (by intravenous infusions) are not accompanied by changes in erythrocyte levels (Wallach *et al.*, 1962). Hemodialysis of hypermagnesemic patients, with magnesium-free or -low dialysates, has had little or no effect on erythrocyte magnesium (Paschen *et al.*, 1971). Under usual circumstances, the red cell membrane permits only slow diffusion of magnesium (Wallach *et al.*, 1962; Ginsberg *et al.*, 1962). This is reflected by the very slow uptake of ^{28}Mg by erythrocytes (Zumoff *et al.*, 1958; Care *et al.*, 1959; Aikawa *et al.*, 1960c; Rogers, 1961; Ginsberg *et al.*, 1962; Aikawa, 1965; Hilmy and Somjen, 1968).

It has long been recognized that erythrocyte magnesium levels do not fall as quickly or as much as does plasma magnesium in acute magnesium deficiency (Tufts and Greenberg, 1937). However, lesser degrees of magnesium deficiency, if prolonged, can cause profound drops in erythrocyte magnesium, to half control values (Elin *et al.*, 1971a,b). Most data indicate that erythrocyte magnesium levels reflect: (1) the magnesium status at the time of erythropoiesis (Tufts and Greenberg, 1937; MacIntyre *et al.*, 1961; Dunn and Walser, 1966; Walser, 1967; Hellerstein *et al.*, 1970; Elin *et al.*, 1971a,b) and the age of the red cells (Henriques and Orskov, 1939; Bang and Orskov, 1939; Dahl, 1950; Bernstein, 1959; Ginsberg *et al.*, 1962).

Thus, the erythrocyte magnesium level is dependent, more on the age mix of the cells in the sample studied, than on the magnesium status at the time it is taken.

A.2.2. Skeletal Muscle Magnesium

Analyses of skeletal muscle biopsies has been recommended as a more useful clinical index of intracellular magnesium than erythrocyte or plasma magnesium (MacIntyre *et al.*, 1961; Dunn and Walser, 1966; Seller *et al.*, 1966; Walser, 1967; Lim *et al.*, 1969a,b; Drenick *et al.*, 1969; Lim and Jacob, 1972a,b). The values for normal human skeletal muscle magnesium are similar to those for normal myocardium (Lim *et al.*, 1969b; Bertrand, 1967; Tipton and Cook, 1963). (For tabulation of data from cattle, horses, pigs, dogs, and rodents, see Walser, 1967.) However, the muscle magnesium levels in experimental animal and human magnesium deficiencies and in clinical magnesium deficiency do not always indicate loss of magnesium. In many studies of acute magnesium deficiency, muscle levels remained essentially unchanged, or decreased only slightly (Cunningham, 1936a; Watchorn and McCance, 1937; Cotlove *et al.*, 1951; Blaxter and Brook, 1954; Morris and O'Dell, 1961, Ko *et al.*, 1962; Welt, 1964; Dunn and Walser, 1966; Bradbury *et al.*, 1968; Woodward and Reed, 1969; Elin *et al.*, 1971).

Because skeletal and cardiac muscle are structurally more comparable than the myocardium is to other tissues, and the magnesium levels in the two tissues are similar (Tipton and Cook, 1963; Wallach *et al.*, 1966a,b, 1967; Lazzara *et al.*, 1963; Walser, 1967), muscle biopsies would seem to provide a useful index of myocardial magnesium levels. However, the exchangeability of skeletal muscle magnesium is much slower than is that of more metabolically active tissues, such as the heart, kidneys, and liver (Aikawa, 1963; Gilbert, 1960; Review: Walser, 1967) (Table A-4). Furthermore, young animals show lower levels of muscle magnesium more rapidly when magnesium deficient than do older animals (Tufts and Greenberg 1937b; Cotlove *et al.*, 1951; MacIntyre and Davidsson, 1958; Morris and O'Dell, 1961; Smith *et al.*, 1962) and greater losses are seen in chronic than in acute deficiencies (MacIntyre *et al.*, 1961; Montgomery 1960, 1961a; Booth *et al.*, 1963; Whang and Welt, 1963). It is possible that the failure of skeletal muscle magnesium to show a significant response to acute deficiency might reflect a high percentage of tightly bound magnesium in skeletal magnesium (Elin *et al.*, 1971).

Since cardiovascular and renal tissues are vulnerable to damage caused by acute and chronic magnesium deficiencies, it is important to select a tissue for analysis that is more likely than are plasma, red cells, or muscle to reflect the magnesium status of those organs.

A.2.3. White Blood Cell Magnesium Determinations

It seems likely that leukocytes, which are the most readily available nucleated, metabolically active cells, should provide a more reliable index of magnesium levels of such tissues as the heart and kidneys than the serum, erythrocytes, or skeletal muscle. Lymph nodes and spleen, for example, have magnesium exchangeability, in terms of speed of uptake of the isotope and the concentration attained by 24

TABLE A-4. Exchangeability of ^{28}Mg in Selected Tissues

Tissue	Speed of uptake (hr)			Estimated content (mEq/liter)	Calves[d]		Cows[d]	
	Rats[a,b]	Rats[a,c]	Dogs[a]		Speed of uptake (hr)[a]	Count at 24 hr	Speed of uptake (hr)[a]	Count at 24 hr
Myocardium	3	2–8	9–24	25.3	3–6	1.64	1–3	1.05
Kidney	3	4	0.1–4	13.6	0.5–3	1.82	0.5	1.75
Liver	3	6–12	2.5–24	17.6	1–6	1.82	3	1.22
Lymph nodes		4	—	—	—	—	—	—
Spleen				17.9	3–6	1.07	0.5–3	0.70
Skeletal muscle	20% in 7–24	to 24	16–24	11.8	Slow	0.23	Slow	0.08
Erythrocytes	45% in 7							
Bone	—	Cumulative; to 24	—	9.9	—	—	—	—

[a]Relative specific activity (R.S.A.) = activity of tissue ^{28}Mg/plasma ^{28}Mg.
[b]Rogers and Mahan (1959) and Rogers (1961).
[c]Aikawa *et al.* (1959).
[d]Rogers *et al.* (1964).

hours, closest to that of heart, kidneys, and liver. We are attempting to develop a procedure for isolating white blood cells, by a means that does not traumatize the membranes, and that will be adaptable to laboratories lacking sophisticated equipment (Ross *et al.*, 1976/1980). In our first venture, we analyzed the total white cell isolate, using a modification of the Boyum (1968) procedure (dextran/hypaque sedimentation), without attempting to separate the small and large mononuclear cells from the polymorphonuclear cells. We have now simplified, somewhat, a time-consuming, cumbersome procedure that has the intrinsic defect of analyzing mixed cells, and are studying lymphocyte magnesium levels (Ross, Seelig, and Berger, in preparation). A similar method has been used by M. P. Ryan and his colleagues in monitoring lymphocyte magnesium levels in patients with congestive heart failure (Counihan *et al.*, 1978a,b). Since there is no standard procedure, nor standard values for white blood cell magnesium, listing our values would be premature until considerably more data have been accrued.

A.3. Percentage Retention of Parenteral Magnesium Loads

The most practical means of evaluating the magnesium status relatively quickly, and with facilities that are readily available, is the determination of 24-hour urinary magnesium output before and after a magnesium load. (We have already discussed possible risk of magnesium loading in the presence of hypercalcemia. Renal failure also militates against a test that might result in marked hypermagnesemia.)

Fitzgerald and Fourman (1956) found that two volunteers, who retained almost none of injected magnesium, as the sulfate, during a control period of adequate magnesium intake, retained 25% and 42% of parenterally administered magnesium (49 and 82 mEq over 2 and 3 days, respectively). Patients whose chronic magnesium deficiency secondary to steatorrhea might have been missed on the basis of their serum magnesium levels (which were 1.39, 1.67, 1.69, and 1.75 mEq/liter), retained 37% to 79% the first 24 hours after receiving 84 mEq of magnesium, given as magnesium sulfate or chloride infusions (Fourman and Morgan, 1962). Thoren (1963) then confirmed earlier observations that normal subjects excrete at least 80–85% of parenterally (i.v. or i.m.) administered magnesium within 24 hours, and found that many of his surgical patients retained considerably more. He concluded that patients who retain more than 20–25% of magnesium (e.g., 20 mEq in two divided doses) are probably repleting a deficit. He commented, however, that patients with magnesium deficiency due to renal magnesium loss, might not be detected by this test. Jones and Fourman (1966) extended the studies of percentage retention of parenteral magnesium infusions (84 mEq) to patients with hypoparathyroidism and found that all seven retained more than 50%, three retaining about 80%.

Application of the magnesium-loading test for proof of suspected magnesium deficiency in infancy was first reported in England (Wilkinson and Harris, 1969; Harris and Wilkinson, 1971). These investigators, who had found magnesium ther-

apy useful over a ten-year period, in the treatment of infants in poor condition because of persistent diarrhea, other causes of loss of gastrointestinal fluids, or who were unresponsive to calcium or other therapy, reported that they were able to prove magnesium depletion in 20 of 29 cases in which the magnesium-loading dose (0.5 mEq/kg) was used, 40% or more of the dose being retained. They administered between 0.24 to 5.71 mEq Mg by mouth in 4, by gastrostomy or nasogastric tube in 2, intramuscularly in 1, and intravenously in 22. Among 9 whose serum magnesium had been measured, it was above the normal range of 1.4 to 1.9 mEq/liter in 2, one of whom retained over half of the test done. The serum magnesium was normal in 4 patients, 3 of whom were magnesium deficient. All 3 with hypomagnesemia retained over 70% of the test dose. Caddell *et al.* (1973b) and Cadell and Olson (1973) similarly found that the lowest magnesium plasma levels (in 40 babies with kwashiorkor or marasmus or both) were correlated with the highest magnesium retentions, and that some with normal plasma magnesium levels had high retentions. These investigators did not find low preload magnesium urinary excretion to be a helpful guide; 7 of 25 who excreted less than 1 mEq of magnesium per 24 hours retained a mean of only 23.3% of the magnesium load and clinical magnesium deficiency was not diagnosed. Caddell (1975) and her colleagues (Caddell and Olson, 1973; Caddell *et al.*, 1973b, 1975a; Byrne and Caddell, 1975) have evaluated magnesium-load test in neonatal, normal, and low-birth-weight infants and infants during the first few months of life, and designed a shorter test *(infra vide)*, as well as using this test to evaluate the magnesium status postpartum (Caddell *et al.*, 1973a, 1975b). In the magnesium-loading studies of postpartum women, Caddell *et al.* (1973, 1976) found that among Thai women with ample magnesium intakes, the postpartum women retained more magnesium than did nulliparous young women, but not nearly as much as did many of the American women (particularly young multiparous women). However, except for women with plasma magnesium levels below 1.2 mEq/liter, the amount of magnesium retained was not reflected by the plasma levels.

A.3.1. Recommended Procedures for Determining Percentage Retention of Parenteral Magnesium Load

Although, ideally, it is desirable to obtain a 24-hour urine sample for base-line magnesium levels (and for creatinine output to permit evaluation of renal function before and after the magnesium load), the clinical status may be too precarious to permit so long a delay before instituting magnesium therapy when there are signs suggesting its depletion. In that event, a single pretreatment urine and blood sample for magnesium and creatinine levels must suffice, and the 24-hour posttreatment urine collected for analysis. Those, whose test is part of a diagnostic procedure, should have magnesium laxatives and antacid withheld for 48 hours before the pretreatment collection and during the test. If medically acceptable, withhold strong magnesium-wasting diuretics, such as furosemide or ethacrynic acid, or substitute a thiazide diuretic for the duration of the test.

A.3.1.1. Adults: Intramuscular Load

After collecting urine for 24 hours and taking a blood sample for magnesium and creatinine levels, 2 ml of 50% $MgSO_4$ (100 mg of magnesium) should be injected deep into each buttock. Collect the next 24-hour urine, and draw blood at the end of the collection period for magnesium and creatinine analysis. It is often of value to have the specimens analyzed for additional electrolytes, such as calcium, sodium, potassium, and phosphorus. Subtract the amount of magnesium in the preload 24-hour urine from that in the postload 24-hour urine and calculate the percentage of the load that was retained.

A.3.1.2. Adults: Intravenous Load

The procedure is as above, except that the magnesium load (0.4 to 0.5 mEq/kg, as magnesium sulfate or magnesium chloride, diluted in 100 cc 6% dextrose in water or 0.9% saline) is given over a 45-minute period.

A.3.1.3. Infants: Intravenous Load

The procedure is as for adults, with the time for delivery extended to 1–1½ hours. Harris and Wilkinson (1971) caution that no talcum powder should be used during collection periods, and that the collecting vessel (i.e., plastic bag) should be rinsed at least six times with de-ionized water.

A.3.1.4. Infants: Intramuscular Load

Caddell *et al.* (1975) and her co-workers (Byrne and Caddell, 1975; Caddell *et al.*, 1975a) have modified the test to allow for shorter collection periods for infants up to 6 months of age. Preload plasma cations and 8-hour urinary levels of magnesium, calcium, potassium, sodium, and creatinine are determined. An intramuscular injection of 50% sulfate (0.12 ml/kg, equivalent to 0.49 mEq/kg of body weight) is given to infants whose plasma magnesium levels do not exceed 2.0 mEq/liter, who are well hydrated, and who have good renal function. Caddell cautions that although even premature neonates can excrete an excessive magnesium load (as has been shown by the rapid drops of serum magnesium levels in symptomatic hypermagnesemic infants born to eclamptic mothers given high doses of magnesium within 24 hours of delivery) (Brady and Williams, 1967; Soka *et al.*, 1972), neonatal infants have immature renal function (Rubin *et al.*, 1949; Wilkinson, 1973). Thus, the risk of producing hypermagnesemia and of reciprocally increasing urinary calcium excretion must be kept in mind. Caddell (1975) has observed that most of the magnesium load was usually excreted during the first 8 hours postload, although in a few instances neonatals excreted more magnesium in the second 8-hour period. The 24-hour reading usually provided a reliable reading of the amount retained. Infants who retained more magnesium had lower plasma levels of magnesium than did those who retained less. For example, full-term infants who retained 80% of the load had preload plasma magnesium levels of 1.50 mEq/liter; the prematures with

plasma magnesium levels averaging 1.59 mEq/liter retained 85.67 ± 2.2 of the load. Those with preload plasma levels of 1.77 and 1.90 meq/liter (full term and premature) retained 28.2 ± 3.04 and 21.5 ± 0.89, respectively (Byrne and Caddell, 1975). However, despite the grouped evidence correlating low plasma magnesium levels with high retentions, the authors pointed out that in their series individual instances of magnesium deficiency of infancy would have been infrequently diagnosed on the basis of the plasma values alone. The infants had higher plasma magnesium levels at the end of the load test than at the beginning, an effect attributed to normalization of low initial values and incomplete renal clearance of the load (Caddell, 1975).

A.3.2. Evaluation of Renal Handling of Magnesium

Freeman and Pearson (1966) reported a patient with renal magnesium wastage, detected because the amount of (preload) magnesium excreted was inappropriately high in view of her hypomagnesemia, and who exhibited only partial renal conservation of magnesium on moderate reduction of her magnesium intake. They pointed out that a prerequisite for the magnesium-loading test is normal renal mechanisms for conserving magnesium.

Parfitt (1976/1980) has developed a model for assessing the tubular reabsorption of magnesium that plots data for $U_{Mg}V/GFR$ against the plasma magnesium level. He points out that short-term renal conservation of magnesium passively reflects the fall of plasma magnesium levels. Long-term depletion results in active renal magnesium conservation, which might result from an increase in its maximum tubular (Tm) reabsorption. However, in a prolonged magnesium depletion study (Shils, 1969a), no increase in tubular magnesium reabsorption was observed, and a maximum Tm has, in fact, been demonstrated for magnesium (Barker *et al.*, 1959; Averill and Heaton, 1966; Massry *et al.*, 1969). Thus, agents that cause renal magnesium wastage do so by lowering Tm_{Mg}/GFR transiently or permanently. In the case of the metabolic abnormality that interferes with renal tubular magnesium reabsorption, the Tm_{Mg}/GFR is abnormally low.

TABLE A-5A. Infantile Ischemic Heart Disease: Stillbirth through One Month (Individual Case Reports, or Data Specified Individually in Tables)

Case No.	Age (days)	Gestational factors (maternal or fetal)[a]	Infantile findings (first day/2–30 days)[b]	SD/TI[c]	Pathologic findings (arteries/heart)[d]	ABN[e]	Reference
1	14	N.D.[f]	LBW/↑ CR	N.D.	AS-Ao,Pu;IM-Th;Ca/M-N;L;Ca	N.D.	Durant (1899)
2	21	N.D.	N.D.	N.D.	—/M-Ca	N.D.	Jakobsthal (1900)
3	<1	N.D.	LBW, ↓ O_2/RD	N.D.	Ao-At/CE;M-F;En-F	N.D.	Stiassny (1901)
4	0	N.D.	LBW/—	N.D.	—/M-F;En-F;Pl	N.D.	Ruge (1905)
5	<1	N.D.	N.D.	N.D.	Ao-At/M-F;En-F;Th;Va	N.D.	Monckeberg (1907)
6	<1	N.D.	N.D.	N.D.	—/M-F;En-F,Th;Va	N.D.	Monckeberg (1907)
7	<1	N.D.	N.D.	N.D.	Ao-At/En-F,Th;Va	N.D.	Kockel (1909)
8	<1	N.D.	N.D.	N.D.	—/M-F;En-F,Pl	N.D.	Ganeff (1910)
9	2	H	RD/RD,CF	N.D.	Ao-At,N,El/—	N.D.	Jaffe (1914)
10	3	N.D.	N.D.	N.D.	—/M-F,Ca;En-F,Pl	N.D.	Loesser (1915)
11	5	N.D.	N.D.	N.D.	—/M-F,Ca;En-F,Pl	N.D.	Loesser (1915)
12	3	N.D.	N.D.	+/—	AS(L-C;V);IM,N,Ca/—	N.D.	Surbek (1917)
13	2	N.D.	N.D.	N.D.	Pu-At/M-Ca;En-F,Th	N.D.	Von Zalka (1921)
14	5	N.D.	N.D.	N.D.	Ao-At/En-F,Th;Va	N.D.	Philpott (1928)
15	3	CS	—/AP, ↑ CR	N.D.	AS(L-C)-IM/—	N.D.	Kissane & Fidler (1931)
16	1	H	LBW/RD,CF	N.D.	AS(L,Sm-C)-IM,Ca;Ao-At/—	K-N,Ca	IFF (1931)
17	<1	N.D.	N.D.	N.D.	AS(L-C);Ao-At/M-Ca;En-F,Th	N.D.	Bellet & Gouley (1932)
18	<1	N.D.	LBW/—	N.D.	—/M-N,Ca	B	Diamond (1932)
19	3	N.D.	—/↓ O_2	N.D.	Ao-At/En-F,Th	N.D.	Farber & Hubbard (1933)
20	3	(SA)	—/↓ O_2	N.D.	—/M-Ca,L	N.D.	Farber & Hubbard (1933)
21	2	N.D.	N.D.	N.D.	AS(L-C)-IM/CE;M-N,Ca;En-F;Th;Va	N.D.	Stohr (1934)
22	9	N.D.	N.D.	N.D.	Ao-At/CE;M-N,F,Ca;En-F,Th;Va	N.D.	Stohr (1934)
23	3	N.D.	N.D.	N.D.	Ao-At/CE;M-Ca	N.D.	Wesson & Beaver (1935)
24	<1	I,MB	N.D.	N.D.	AS(Sm-C)-IM;Ao-At/M-F,L;En-F,Th	N.D.	J. Roberts (1936)
25	6	(SA:3)	N.D.	N.D.	AS(SM,L-C;Pu;V)-N/—	B	Kaul (1939
26	4	DL	—/RD; ↓ O_2	N.D.	—/CE;M-F,Ca;En-F,Th	N.D.	Gross (1941)
27	4	N.D.	—/RD	N.D.	AS(L-C)-IM;Ao-At/En-F,Th;Va	N.D.	Rossman (1942)
28	28	N.D.	N.D.	N.D.	—/CE;MI-Dis;N,F	N.D.	Wessman (1942)
29	5	DL	N.D	+/—	—/MI-Dis,N	N.D.	Knop & Bennett (1944)
30	2	(SA);CS	—/RD, ↓ O_2;C; ↑ CR	N.D.	Ao-At;Thr/En-F,Th	N.D	MacGregor & McKinley (1944)
31	>0	H,(SA);PA	↓ O_2/—	N.D.	AS(Sm,L-C,V,G)/—	K-Ca	S. Andersen (1945)
32	<1	N.D.	—/RD;CE	N.D.	AS(V);Thr/CE;En-F,Th;Va	N.D.	Cosgrove &Kaump (1946)

(*continued*)

[a]CS, Caesarian section; DL, difficult labor; FD, fetal distress; FP, frequent pregnancies; H, hydramnios; I, maternal immaturity; MB, multiple birth; PA, placenta abnormal; Rh, Rh incompatibility; (SA), spontaneous abortion history; T, toxemia of preganancy.

[b]An, Anorexia; Ap, apnea; C, convulsions; CE, cardiac enlargement; CF, cardiac failure; ↑ CR, tachycardia; ECG, conduction or rhythm abnormality; GF, growth failure; Le, lethargy; LBW, low birth weight; MI, myocardial infarct; ↓ O_2, hypoxia, cyanosis; P, pallor; RD, respiratory distress; S, syncope; Tr, tremor, tetany, irritability; Thr, thrombosis; Vo, vomiting.

[c]Sudden death (+)/duration of terminal illness.

[d]Ao, Aorta; AS, arteriosclerosis [C, coronary (L, large, Sm, small); Ce, cerebral; G, generalized; Pe, peripheral; Pu, pulmonary; V, visceral]; At, atresia, coarctation, narrowed; Ca, calcium deposition; CE, cardiomegaly; El, elastica (degeneration); En, endocardial; F, fibrosis; I, infarction (Dis, disseminated; Ma, massive); Im, intimomedial; L, lipid deposition; M, myocardial; N, necrosis; Pa, papillary muscle; Pl, plaques; S, septal abnormality; Th, thickened; Va, valve abnormality.

[e]Abnormality of B, bone; K, kidney.

[f]N.D., No data.

TABLE A-5A. (*Continued*)

Case No.	Age (days)	Gestational factors (maternal or fetal)[a]	Infantile findings (first day/2–30 days)[b]	SD/TI[c]	Pathologic findings (arteries/heart)[d]	ABN[e]	Reference
33	3	N.D.	—/RD, ↓ O_2;CE	N.D.	—/CE;En-F,Th	N.D.	Cosgrove & Kaump (1946)
34	7	T	—/RD, ↓ O_2	N.D.	—/CE;En-F,Th	N.D.	Cosgrove & Kaump (1946)
35	<1	N.D.	↓ O_2/—	N.D.	AS(L-C);Thr/—	N.D.	Stryker (1946)
36	>0	MB	↓ O_2/—	N.D.	AS(L-C;Pu)-IM,Ca/MI-Dis;N;Ca	N.D.	Stryker (1946)
37	3	N.D.	—/V,An	+/—	AS(Sm-C;Pu)-IM,N/CE;MI-S	N.D.	Ravich & Roseblatt (1947)
38	<1	FP;FD;DL	LBW; ↓ O_2/RD, ↓ O_2	N.D.	L-C;Thr/MI-Dis	N.D.	Ravich & Rosenblatt (1947)
39	1	N.D.	LBW/RD; ↓ O_2	N.D.	Ao-At/En-F,Th;VA	N.D.	J. Craig (1949)
40	<2	N.D.	—/RD; ↓ O_2	N.D.	—/M-N;Ca;En-F,Th	N.D.	J. Craig (1949)
41	2	N.D.	—/RD; ↓ O_2	N.D.	—/En-F,Th;Va	N.D.	J. Craig (1949)
42	3	N.D.	—/RD; ↓ O_2;P,Le;CE/ECG	N.D.	—/En-F,Th;Va	N.D.	J. Craig (1949)
43	3	N.D.	—/RD; ↓ O_2;CE	N.D.	—/En-F,Th	N.D.	J. Craig (1949)
44	3	N.D.	—/RD; ↓ O_2;S	N.D.	—/En-F,Th	N.D.	J. Craig (1949)
45	6	MB	—/ ↓ O_2;CF	N.D.	—/M-N,F;En-F,(Pa);Thr;Va	N.D.	J. Craig (1949)
46	7	N.D.	—/ ↓ O_2	N.D.	Ao-At/M-F;En-F	N.D.	J. Craig (1949)
47	8	N.D.	—/RD; ↓ O_2	N.D.	—/M-F;En-F	N.D.	J. Craig (1949)
48	9	N.D.	—/RD; ↓ O_2;P	+/7 hr	Ao-At/En-F,Th	N.D.	J. Craig (1949)
49	13	MB	—/ ↓ O_2;ECG	N.D.	—/En-F,Th	N.D.	J. Craig (1949)
50	0	H	LBW/—	N.D.	—/M-N;En-F,Th	N.D.	Prior & Wyatt (1950)
51	7	N.D.	—/RD; ↓ O_2	+/—	—/En-F,Th;Va	N.D.	Prior & Wyatt (1950)
52	23	N.D.	—/RD; ↓ O_2;CF	+/—	—/En-F,Th;Va	N.D.	Prior & Wyatt (1950)
53	<1	DL	RD; ↓ O_2/—	N.D.	AS(L-C)/M-Dis;N,Ca,F;En-F,Th	N.D.	Blumberg & Lyon (1952)
54	<1	N.D.	LBW;RD; ↓ O_2/ ↓ CR	N.D.	—/CE;M-Dis;N,Ca;En-F,Th	N.D.	Blumberg & Lyon (1952)
55	4	DL	—/ ↓ O_2;ECG	+/3 d	AS(L-C;V)/MI-Mas,N;IM;Thr	N.D.	Nestor *et al.* (1953)
56–61	4	N.D.	—/RD(6)	N.D.	AS(L-C)-N,IM;AS-V/(6)	N.D.	Cochrane & Bowden (1954)
62	28	FP	—/V,An,GF	+/—	—/En-F,Th	N.D.	Kelly & Andersen (1955)
63	4	N.D.	—/RD; ↓ O_2	N.D.	—/En-F,Th;Va	N.D.	Horley (1955)
64	5	N.D.	—/RD; ↓ O_2	N.D.	—/En-F,Th;Va	N.D.	Horley (1955)
65	8	N.D.	—/RD; ↓ O_2	N.D.	Ao-At/En-F,Th	N.D.	Horley (1955)
66	24	N.D.	—/RD; ↓ O_2;V;Thr	N.D.	AS(Sm,L-C;Pu;Ce;V)-IM;Th/CE;M-N	N.D.	Weems & Marin (1956)
67	<5	MB	N.D.	N.D.	—/M-Dis N	N.D.	Ahvenainen & Hjelt (1956)
68	6	MB	N.D.	N.D.	—/M-Dis N	N.D.	Ahvenainen & Hjelt (1956)
69	6	N.D.	↓ O_2/RD; ↓ O_2	N.D.	Ao-At/En-F,Th	N.D.	Ahvenainen & Hjelt (1956)
70	10	N.D.	—/S, ↑ CR	+/3 d	—/M-Dis N	N.D.	Ahvenainen & Hjelt (1956)
71	10	N.D.	—/CF,ECG(MI)	+/1 d	Thr/M-Dis N	N.D.	Ahvenainen & Hjelt (1956)
72	10	N.D.	—/RD; ↓ O_2;S	+/5 d	—M-N	N.D.	Ahvenainen & Hjelt (1956)
73	10	CS	—/ ↓ O_2	N.D.	—/SubEn-N	N.D.	Ahvenainen & Hjelt (1956)
74	16	CS	RD	N.D.	—/M-Dis N	B	Ahvenainen & Hjelt (1956)
75	<1	PA	↓ O_2;CE	N.D.	-M-N(Pa)	N.D.	Richart & Benirschke (1959)
76	7	N.D.	↓ O_2/ ↓ O_2;RD;Ap/ECG	+/1 d	AS(C)Thr/M-Dis N	N.D.	Richart & Benirschke (1959)
77	<1	(SA)	LBW;Tr/ ↓ O_2;ECG	N.D.	AS(L-C)-IM,Thr;L/MI-Mas	N.D.	Gault & Usher (1960)
78	4	N.D.	—/ ↓ O_2;RD;CF	+/2 d	AS(L-C)-IM,N;Ao-At/CE;MI-Mas;En-F,Th	N.D.	Clapp & Naeye (1961)
79	0	N.D.	N.D.	N.D.	AS(G)/—	N.D.	Falkmer (1961)
80–90	0	Rh(11)	N.D.	N.D.	—/M,Pa-N,SubEn;En-F,Pl(11)	N.D.	Hogg (1962)
91–105	<1–6	Rh(14)	N.D.	N.D.	—/M-Dis N,Pa SubEn;En-F,Pl(14)	N.D.	Hogg (1962)

106	0	H,(SA-8)	LBW/ –	N.D.	AS(L-C,G)/ –	K-Ca	Ivemark *et al.* (1962)
107	0	H,Pa,FD	LBW/ –	N.D.	AS(L-C,G)/ –	N.D.	Ivemark *et al.* (1962)
108	3	FP;PA	–/S,V, ↓ O_2	N.D.	AS(Ao,V)-N,Thr/ –	N.D.	Naeye *et al.* (1964)
109	<1	Rh,T;FD	LBW; ↓ O_2,CE;ECG/ –	N.D.	AS(Sm-C,Pu,V,G)-IM/ –	K-Ca	Bacon (1964)
110	31	FD(MI)	–/RD; ↓ O_2;CE;ECG	+/2 wk	–/CE;MI-Mas	N.D.	Coleman & MacDonald (1962)
111	0	N.D.	N.D.	N.D.	–/MI-Mas	N.D.	Franciosi & Blanc (1965)
112	4	N.D.	N.D.	N.D.	–/MI-Mas,F	N.D.	Blanc *et al.* (1966)
113	9	N.D.	N.D.	N.D.	–/MI-Mas,F	N.D.	Blanc *et al.* (1966)
114	0	N.D.	N.D.	N.D.	AS(Sm-C)-IM,N/SubEn-N	N.D.	Oppenheimer & Esterly (1966)
115	0	N.D.	N.D.	N.D.	AS(L-C)-IM/MI-SubEn,N,Ca,F	N.D.	Oppenheimer & Esterly (1966)
116	<1	T	RD; ↓ O_2/ –	N.D.	AS(Sm,L-C;IM,N;Ao-At/M-F;En-F,Pl	N.D.	Oppenheimer & Esterly (1966)
117	14	N.D.	LBW, ↓ O_2/ –	N.D.	Ao-At;N,Ca/En-F,Pl;Va	N.D.	Oppenheimer & Esterly (1966)
118	1	FD;PA	N.D.	N.D.	–/M-N,F,Ca	N.D.	Esterly & Oppenheimer (1966)
119	1	N.D.	N.D.	N.D.	AS(L-C)/M-N,Ca;Va;En-F,Pl,Th	N.D.	Esterly & Oppenheimer (1966)
120	1	FD;ECG	N.D.	N.D.	–/M-Ca;En-F,Pl	N.D.	Esterly & Oppenheimer (1966)
121	2	FD;PA	N.D	N.D.	AS/M-N;Ca,F	N.D.	Esterly & Oppenheimer (1966)
122	<1	FD;PA	RD; ↓ O_2	N.D.	–/M-N;Ca	N.D.	Esterly & Oppenheimer (1966)
123	<1	N.D.	N.D.	N.D.	AS(Sm,L-C)N/M-N,Ca	N.D.	Esterly & Oppenheimer (1966)
124	2	N.D.	N.D.	N.D.	AS(L-C)-IM,Ca/M-Ca	N.D.	Esterly & Oppenheimer (1966)
125	2	N.D.	N.D.	N.D.	–/M-N;En-F,Pl	N.D.	Esterly & Oppenheimer (1966)
126	3	FD;ECG	N.D.	N.D.	–/M-F;En-F,Pl	N.D.	Esterly & Oppenheimer (1966)
127	2	N.D.	N.D.	N.D.	–/M-N,F,Ca	N.D.	Esterly & Oppenheimer (1966)
128	3	N.D.	N.D.	N.D.	AS(Sm,L-C)-Ca/M-N,F,Ca;En-F,Pl	N.D.	Esterly & Oppenheimer (1966)
129	4	N.D.	N.D.	N.D.	–/M-N	N.D.	Esterly & Oppenheimer (1966)
130	5	Rh,DI	RD; ↓ O_2	N.D.	–/M-N	N.D.	Esterly & Oppenheimer (1966)
131	5	N.D.	N.D.	N.D.	–/En-F,Pl,Th;Va	N.D.	Esterly & Oppenheimer (1966)
132	7	T,DL	N.D.	N.D.	AS(IOC)-IM,L/M-N	N.D.	Esterly & Oppenheimer (1966)
133	7	T,DL	N.D.	N.D.	C(Anom)/M-N	N.D.	Esterly & Oppenheimer (1966)
134	<2	N.D.	N.D.	N.D.	AS(L-C)/Ao-At	N.D.	Esterly & Oppenheimer (1966)
135	<2	I	N.D.	N.D.	–/M-N	N.D.	Esterly & Oppenheimer (1966)
136	<2	N.D.	N.D.	N.D.	–/M-N	N.D.	Esterly & Oppenheimer (1966)
137	<2	N.D.	N.D.	N.D.	AS(Sm-C)-L;Pu-At/M-N	N.D.	Esterly & Oppenheimer (1966)
138	14	N.D.	–/RD	N.D.	–/M-N	N.D.	Esterly & Oppenheimer (1966)
139	14	N.D.	–/RD; ↓ O_2	N.D.	AS(L-C);Ao-At/M-N,Ca;En-F,Pl,Th	N.D.	Esterly & Oppenheimer (1966)
140	21	N.D.	N.D.	N.D.	–/M-N	N.D.	Esterly & Oppenheimer (1966)
141	21	N.D.	N.D.	N.D.	AS(L-C)/M-F;En-F,Pl,Th	N.D.	Esterly & Oppenheimer (1966)
142	21	N.D.	N.D.	N.D.	–/M-N,Ca	N.D.	Esterly & Oppenheimer (1966)
143	11	N.D.	N.D.	N.D.	L-C,Thr/S	N.D.	Oppenheimer & Esterly (1967)
144	11	N.D.	N.D.	N.D.	L-C,Thr/S	N.D.	Oppenheimer & Esterly (1967)
145	14	N.D.	N.D.	N.D.	L-C,Thr;Ao-At	N.D.	Oppenheimer & Esterly (1967)
146	18	N.D.	N.D.	N.D.	C Anom,AS-C/En-F	N.D.	Oppenheimer & Esterly (1967)
147	10	N.D.	–/RD, ↓ O_2;CF,V	+7 d	L-C,Thr/MI-Ma,S;En-F,Pl	N.D.	Bor (1969)
148	28	N.D.	–/RD,V	+1 d	AS(L-C);IM,L/MI-Mas;En-F,Th	N.D.	Bor (1969)
149	12	N.D.	–/Sudden pain	+7 d	Ao-At/En-F,Th;S	N.D.	Bor (1969)
150	7	N.D.	N.D.	N.D.	–/MI-Pa	N.D.	Kangos (1969)
151	14	N.D.	–/MI,ECG	N.D.	–/MI-Pa,Dis,N	N.D.	Kangos (1969)
152	14	N.D.	–/MI-ECG	N.D.	–/MI-Mas,N,Ca	N.D.	Kangos (1969)
153	14	N.D.	N.D.	N.D.	–/MI-Ma,N	N.D.	Kangos (1969)
154	21	N.D.	–/MI-ECG;CF	+1 d	–/CE,M-N,Ca	N.D.	Kangos (1969)
155	24	N.D.	LBW,RD/CE,CF	N.D.	AS(Sm,L-C,G)-IM	N.D.	Parker *et al.* (1971)
156	2	N.D.	N.D.	+	–/M-F;En-F,Pl,Th	N.D.	Elliott (1973)
157	6	N.D.	N.D.	+	M-F;En-F,Pl,Th	N.D.	Elliott (1973)

TABLE A-5B. Infantile Ischemic Heart Disease: Stillbirths to 1 Month[a]

Number	Category	Gestational–birth abnormality	Number surveyed; category	Investigator(s)
23	Abnormal A-V bundle	Fetal distress		Keith (1909)[a]
11	Coronary thickening	Fetal hypoxia; placenta praevia		Clifford (1941)[a]
6	Coronary thickening; intimal cushions		24	Dock (1946)
12	Coronary intimal thickening; frayed elstica; lipid infiltration		30	Fangman and Hellwig (1947)
21	Coronary necrosis (2 with thrombi)	Perinatal hypoxia	220 (9.5% of autopsies, < 3 days of life)	Gruenwald (1949)
43	Endocardial fibroelastosis (EFE)	Abnormal gestation		Craig (1949)
140	EFE; coarctation of aorta		1580 (36% coarctation)	Keith (1956)[a]
18	Elastica damage (13 with intimal thickening; 4 with fat infiltration)	Stillbirths	65 autopsies: stillbirths to 8 days of life	Schornagel (1956)
2	Elastica rupture; no intimal thickening	Prematurity	24 stillbirths	Moon (1957)
32	EFE (26); MI (5)	Stillbirths	Stillbirths to < 4 days of life	Hogg (1962)[a]
1 (or 2)	EFE; conduction abnormality		47 cases EFE (3 hours life) (case cited)	Moller *et al.* (1964)
(c. 100)	Intimomedial thickening (±)		Comparison: Ashkenazim, Yemenites; Bedouins	Neufeld and Vlodaver (1968)
> 3	EFE; tricuspid stenosis		6: 1 day to 6 months	Bryan and Oppenheimer (1969)
	Coronary intimal thickening		9: stillborn to 16 months	
?	Cardiovascular disease	Diabetes mellitus Mother > 38 years	(1:20–1:43 births 1: 84 births)	Mitchell *et al.* (1971)[a]
8	Familial heart block; conducting system abnormality	(Familial)	Study of 1 family; review of 18	Sarachek, Leonard (1972)[a]
97	Cardiomegaly	Prematurity: 45; toxemia: 3; placenta praevia: 1; multiple births: 9	620 low-birth-weight infants (37% with cardiomegaly)	Caldera *et al.* (1975)[a]

[a]From pathology surveys, or individual case data not given.
[b]Reference listed in Table A-7.

Table A-6A. Infantile Ischemic Heart Disease: >1 Month to 2½ Years (Individual Cases)

Case No.	Age (mo)[a]	Gestational factors (maternal or fetal)[b]	Infantile findings (neonatal/later infancy[c])	SD/TI[d]	Pathologic findings (arterial/cardiac)[e]	ABN[f]	Reference
1	*14	N.D.[g]	N.D.	N.D.	—/CE:En-F,Th	N.D.	Hauser (1899)
2	*14	N.D.	N.D.	N.D.	—/CE;En-F,Th;Va-St	N.D.	Hedinger (1904)
3	*14	N.D.	N.D.	N.D.	—CE:En-F,Th:Va-St	N.D.	Oberndorfer (1906)
4	*4	N.D.	N.D.	N.D.	AS(L-C):Ca/—	N.D.	Surbek (1917)
5	*3	N.D.	LBW/GF:MR	N.D.	AS(G):Ca/—	B	Johansson (1921)
6	*3	N.D.	N.D.	N.D.	—/SubEn-N:En-F,Th	N.D.	Steiner & Bogin (1928)
7	*15	N.D.	—/↓O_2;RD;Co	+/2 wk	AS(Sm,L-C)IM/M-N,F(Dis),En-F,Th	N.D.	Stoloff (1928): Kugel-Stoloff (1933)
8	*<3	N.D. (Familial)	—/↓O_2;RD;P:CE	+/4 d	AS(L-C)IM,Ca/SubEn-F;S;En-F,Th	N.D.	Crawford & Weiss (1929)
9	*18	N.D.	—/Ap;Tr;P;Le	+/6 wk	AS(L-C;G)IM;Thr/M-F(Dis)	N.D.	McMichael (1929)
10	*2	(Influenza)	N.D.	+/—	AS(L,Sm−C)IM,Ca:(Ao,Pu,G)/—	N.D.	Hughes & Perry (1929)
11	*6	N.D.	—/V,An,GF,MR	N.D.	—/M-N	K	Putscher (1929)
12	*12	N.D.	—/RD,Ap,+CE	+/4 hr	AS(L-C)L;Pl/SubEn-N;En-F,Th	N.D.	Ramsay & Crumrine (1931)
13	*27	N.D.	—/V,An,GF,MR,↑BP,Ca,L	N.D.	AS(Sm-C,Ce,V,G):IM,Ca/—	B,K	Lightwood (1932)
14	*30	N.D.	↓O_2,C/RD(term.);CE	N.D.	—/M(Pa):SubEn-N,F,Ca	N.D.	Farber & Hubbard (1933)
15	*8	N.D.	—/An,V	+/2 wk	—/M-N(Dis),F	K	Farber & Hubbard (1933)
16	*6	N.D.	—/Ap(term.)	+/1 d	AS(Sm,L-C)IM/M-F(Dis)	K	Farber & Hubbard (1933)
17	*3	N.D.	—/RD(term.),CE(term.)	+/2 hr	AS(Sm,L-C)IM/M-F(Dis)	K	Farber & Hubbard (1933)
18	*4	N.D.	—/Sudden pain	+/8 hr	AS(Sm-C)IM/MI(Dis);En-F,Pl	N.D.	Farber & Hubbard (1933)
19	*3	N.D.	—/CE(term.)	+/—	AS(Sm-C)IM/En-F,Pl	N.D.	Farber & Hubbard (1933)

(*continued*)

[a]Single asterisk indicates age at death. Double asterisk indicates age at time of report.

[b]CS, Caesarian section; DL, difficult labor; ECG, (fetal) conduction abnormalities; FD, fetal distress; FP, frequent pregnancies; H, hydramnios; I, maternal immaturity; MB, multiple birth; PA, placental abnormality; Rh, Rh incompatibility; SA, history of spontaneous abortions; T, toxemia of pregnancy.

[c]An, Anorexia; Ap, apnea; C, convulsions; CE, cardiac enlargement; CF, cardiac failture; ↑CR, tachycardia; ↓CR, bradycardia; D, deafness; ECG, conduction, rhythm abnormalities; F, facies abnormal; GF, growth failure, weight loss; Ir, irritability, tremor, tetany; Le, lethargy; LBW, low birth weight; MI, myocardial infarction; MR, mental retardation; ↓O_2, hypoxia, cyanosis; P, pallor; RD, respiratory distress; S, syncope; Thr, thrombosis; V, vomiting; ↑BP, hypertension; ↑Ca, hypercalcemia; ↑L, hyperlipemia.

[d]Sudden death (+)/duration of terminal illness.

[e]Ao, aorta; AS, arteriosclerosis [C, coronary (Sm, small; L, large); G, generalized; Pu, pulmonary; V, visceral; Ce, cerebral]; Ca, calcium deposition; CE, cardiac enlargement; El, elastica degeneration; En, endocardial; F, fibrosis; IM, intimomedial thickening; Li, lipid deposition; M, myocardial; MI, myocardial infarction; N, necrosis, infiltration; Pa, papillary muscle; Ol, plaques; Se, septal abnormality; St, stenosis, atresia, coarctation; Va, valve (Mas, massive; Dis, disseminated, multifocal).

[f]Abnormality of B, bone; K, kidney.

[g]N.D., No data.

TABLE A-6A. (*Continued*)

Case No.	Age (mo)[a]	Gestational factors (maternal or fetal)[b]	Infantile findings (neonatal/later infancy[c])	SD/TI[d]	Pathologic findings (arterial/cardiac)[e]	ABN[f]	Reference
20	*3	N.D.	N.D.	N.D.	AS(G)/—	B,K	Smyth & Goldman (1934)
21	*<5	N.D.	↓ O_2,RD/CE	+/6 d	Ao-At/En-F,Th;En-F,Pl	N.D.	Weinberg & Himmelfarb (1934)
22	*<4	FP(?)	LBW/RD, ↓ O_2,CE(term.)	+/3 d	—	N.D.	Weinberg & Himmelfarb (1934)
23	*5	T,(SA-3),FP	—/ ↓ O_2,CE,Thr	N.D.	—/En-F,Pl:Va-St	N.D.	Farber & Hubbard (1933)
24	*12	N.D.	—/An,V,GF,Co	N.D.	AS(G)-Ca/—	K	Lightwood (1935)
25	*24	FP	—/CE,CF, ↑ CR,ECG, ↑ BP	+/3 wk	AS(Sm-C)-IM,Thr/M,SubEn-(Dis);En-F,Th	K	Taussig & Remsen (1935)
26	*13	N.D.	—/RD(term.),CE,CF(term.)	+/7 wk	AS(Sm-C)IM/M-N,F(Dis),S	N.D.	Mahon (1936)
27	*30	N.D.	—/GF, ↑ CR	+/1 wk	AS(Sm-C)IM/M-F(Dis);Va-St;En-F,Th	N.D.	Mahon (1936)
28	*28	N.D.	—/GF,An,V	+/—	AS(Sm-C,Pu,V)/M-Ca	K	Ross & Williams (1939)
29	*24	N.D.	—/V,Tr	+/4 hr	AS(L-C,Pu,V)IM,Ca/M-F(Dis);En-F,Pl,Th	N.D.	Baggenstoss & Keith (1941)
30	*18	(SA),FP(?)	C, ↓ O_2/RD(term.)S,P,ECG	+/4 wk	AS(L-C)Ca,Thr/M(Pa)-N	K	Van Creveld (1941)
31	*24	N.D.	—/ ↓ O_2(term.)	+/—	AS(L-C)Ca/—	K	Van Creveld (1941)
32	*6	(SA)	↓ O_2,C/An,V,Tr,GF, ↑ L	N.D.	AS(L-C,V,G):N,El,Ca.Thr/M-N,F,Ca(Dis)	B,K	Andersen & Schlesinger (1942)
33	*6	N.D.	—/C, ↑ BP, ↑ L	+	AS(L-C,G)N,El,Ca/M-N,Ca(Dis)	K	Andersen & Schlesinger (1942)
34	*<2	N.D.	—/ ↓ O_2,RD(term.)	+/1 d	—/M(Pa)-N; —/En-F,Th	N.D.	Weisman (1942)
35	*<6	N.D.	—/ ↓ O,RD(term.)	+/1 d	—/M-L;En-F,Th:Va	N.D.	Sano & Anderson (1942)
36	*<3	N.D.	—/ ↓ O_2,RD,Ap(sudden)	+/1 d	AS(L-C,Pu,V,G),IM,Ca/—	N.D.	Field 1946)
37	*11	T,(SA-6)	—/ ↓ O_2,RD,V,Le	+/2 d	AS(L-C,V)IM/M-N,Ca,F(Dis)	N.D.	Scott & Miller (1946)
38	*3	N.D.	LBW/Le,Tr,ECG(sudden)	+5/ hr	—/M-N;En-F,Th	N.D.	Cosgrove & Kaump (1946)
39	*<6	N.D.	—/An,V	+/1 wk	—/En-F,Th	N.D.	Cosgrove & Kaump (1946)
40	*<19	N.D.	—/RD(term.)	+/2 hr	—/En-F,Th;Va-St	N.D.	Cosgrove & Kaump (1946)
41	*3	N.D.	—/RD(term.)	N.D.	AS(Sm,L-C)IM,Ca,Thr/M-N(Dis)	K	Stryker (1947)
42	*6	FP;(SA-2)	—/—	+/3 d	AS(Sm-C)Ca/—	N.D.	Stryker (1947)
43	*7	N.D.	—/ ↓ O_2,RD	N.D.	AS(Sm,L-C,Pu,V,Ca:Thr/M-N,F(Dis),CE;En-F,Th	N.D.	Stryker (1947)
44	*<4	T	—/RD;C; ↑ Ca	+/2 d	AS(L-C,Pu,V,G)IM-N,Ca,Thr/CE;M-N,Ca(Dis)	K	Hause & Antell (1947)

45	*2	DL	—/↓O_2;RD;Tr	+/1 d	AS(Sm,L-C,V)/CE:MI-Mas;Thr	K	Menten & Fetterman (1948)
46	*<2	Familial—sibs	—/↓O_2;RD	N.D.	AS(L-C)/—	N.D.	Menten & Fetterman (1948)
47	*<2	Familial—sibs	—/↓O_2;RD	N.D.	AS(L-C)/—	N.D.	Menten & Fetterman (1948)
48	*<6	N.D.	—/↓O_2;RD;An,V,C;CF;↑L,↑Ca	N.D.	AS(L-C,Pu,G);IM,Ca/M-Ca	K	Prior & Bergstrom (1948)
49	*3	T	—/An,V,Le:↓CR	+/7 hr	AS(L-C,V);IM,Ca/MI-Mas	K	Prior & Bergstrom (1948)
50	*3	N.D.	N.D.	N.D.	AS(L-C)Thr/MI-Mas, N,Ca	N.D.	Gorge & Aron (1949)
51	*2	N.D.	—/↓O_2;ECG	+/1 d	AS(Sm-C):IM-N,El/SubEn-Ca;En-F,Th	N.D.	Craig (1949)
52	*2	N.D.	—/RD;C	+/3 hr	L-C(Anom.)/SubEn-F;En-F,Th	N.D.	Craig (1949)
53	*2	N.D.	N.D.	+/2 hr	AS(L-C):IM,N,El/SubEn-N,Ca;En-F,Th	N.D.	Craig (1949)
54	*2	N.D.	—/↓O_2;RD(sudden)	+/1 mo	AS(L-C)IM,N,El/SubEn-N,En-F,Th	N.D.	Craig (1949)
55	*<2	N.D.	—/ECG,CE(term.)	+/2 wk	—/SubEn-N,F;En-F,Th;Va-St	N.D.	Craig (1949)
56	*<3	N.D.	C/↓O_2;C;GF:CF;CE	+/2 d	—/SubEn-N,F:En-F,Th;Va-St	N.D.	Craig (1949)
57	*3	N.D.	—/GF;RD(term.)	+	—/En-F,Th	N.D.	Craig (1949)
58	*3	N.D.	LBW,C/C	N.D.	—/SubEn-F;Va	N.D.	Craig (1949)
59	*<3	N.D.	—/ECG	+/<1 d	—/En-F,Th	N.D.	Craig (1949)
60	*<4	N.D.	—/↓O_2;RD;CE	N.D.	—/SubEn-N;En-F,Th;Va	N.D.	Craig (1949)
61	*4	N.D.	—/RD;HF(term.)	N.D.	—/En-F,Th	N.D.	Craig (1949)
62	*4	N.D.	—/CF(term.)	+/3 d	—/En-F,Th;Va	N.D.	Craig (1949)
63	*<5	N.D.	↓O_2/↓O_2;CF	N.D.	—/SubEn-F;En-F,Th;Va	N.D.	Craig (1949)
64	*5	MB	—/CF(term.)	+/—	—/En-F,Th	N.D.	Craig (1949)
65	*5	N.D.	↓O_2/RD;CF;ECG(term.)	N.D.	Ao-St/M-N;En-F,Th;Va-St	N.D.	Craig (1949)
66	*6	N.D.	↓O_2/↓O_2;ECG	N.D.	—/En-F,Th;Va-St	N.D.	Craig (1949)
67	*5	N.D.	↓O_2/↓O_2	N.D.	—/En-F,Th;Va-St	N.D.	Craig (1949)
68	*9	N.D.	—/↓O_2;RD;CF	3 mo	—/En-F,Th	N.D.	Craig (1949)
69	*9	N.D.	—/↓O_2;RD	4 mo	Ao-St/En-F,Th	N.D.	Craig (1949)
70	*10	N.D.	↓O_2/↓O_2	N.D.	—/En-F,Th	N.D.	Craig (1949)
71	*5	N.D.	—/C,Tr(sudden)	+/3 d	—/M(Pa)-N,Va;En-F,Th;Va-St	N.D.	Prior & Wyatt (1950)
72	*4	N.D.	—/RD,P(sudden)	+/10 d	—/M(Pa)-N,Ca;En-F,Th	N.D.	Prior & Wyatt (1950)
73	*<4	N.D.	—/↓O_2;Tr,P(sudden)	+/2 d	—/M(Pa)-N,Ca;En-F,Th;Va-St	N.D.	Prior & Wyatt (1950)
74	*5	N.D.	—/P	+	—/M(Pa)-N,Ca;En-F,Th;Va-St	N.D.	Prior & Wyatt (1950)
75	*9	N.D.	—/↓O_2;RD;P(sudden)	+/14 d	—/M(Pa),N,Ca;En-F,Th;Va-St	N.D.	Prior & Wyatt (1950)
76	*7	N.D.	—/↓O_2;RD;V,An(sudden)	N.D.	AS(L-C,G);IM,N,Ca/M-N	K	Scheidegger (1950)
77	*5	N.D.	—/CF;CE;↑CR;ECG(MI)(sudden)	+/6 d	AS(Sm-C)(2)/M-N,F(2),Pa(3)	K	Lipman (1951)
78	*3	N.D.	—/Tr,V,ECG(MI)	+/1 d	AS(Sm,L-C)IM,N,El,Ca/SubEn-F,S-F	N.D.	Boldero (1951)
79	*<1	N.D.	↓O_2(7):RD(11):V,An(9);C(3);Le(2);C,Tr(9);CF(5);CE(10);ECG(6)	+(9)/1 d	AS(L-C)(1)/M-N(8) AS(Sm-C)(2)/M-N,F(2),Pa(3) AS(G)(1);IM(1)/SubEn-N,F(3)	N.D.	Blumberg & Lyons (1952)
↑↓	↑↓						
99	*30			8 mo	L(2)/En-F,Th(17) Ao-St(3),Thr(1)/Va(5);Se(2) Pu-St(1)/—		

(continued)

TABLE A-6A. (*Continued*)

Case No.	Age (mo)[a]	Gestational factors (maternal or fetal)[b]	Infantile findings (neonatal/later infancy[c])	SD/TI[d]	Pathologic findings (arterial/cardiac)[e]	ABN[f]	Reference
100	*3	N.D.	—/RD;Shrieks(sudden)	+/—	AS(L-C,V,G):IM-CA/M-N(Dis:Pa:CE	K	Sladden (1952)
101	*18	N.D.	LBW/GF;C	N.D.	AS(L-C,V)-IM,Ca/—	K	Sladden (1952)
102	*18	N.D.	—/P,S(sudden) —/↑CR;ECG(MI)	+/7 hr	AS(Sm,L-C);IM-N,El,L/MI-Mas	N.D.	Wahlgren (1952)
103	*8	N.D.	LBW/↓O_2;GF;P;S	+/10 d	AS(Sm,L-C);IM-N,El,Ca/SubEn-Dis	N.D.	Mant *et al.* (1952)
104	*7	N.D.	—/RD;CR,ECG;↑BP	N.D.	Ao-St	N.D.	Oppenheimer (1953)
105	*10	N.D.	—/RD;C;Cardiac Surg.	N.D.	Ao-St; En-F,Th	N.D.	Oppenheimer (1953)
106	*16	N.D.	—/RD;↑BP;CF	N.D.	Ao-St;En-F,Th;Va-St	N.D.	Oppenheimer (1953)
107	*16	N.D.		+/6 d	—/M-Dis	N.D.	Oppenheimer (1953)
108	*7	N.D.	—/GF,Le,Mr,CF;↑BP,↑Ca	N.D.	—/Va-St	B,K	Creery (1953)
109	*24	T,SA,PA	—/CF,ECG	—/1 yr	AS(Ao,L-C)-N,El/M-N(Dis)	N.D.	Nestor *et al.* (1953)
110	*10	N.D.	—/RD,Le,V,An,Tr;CF,↑CR,↑BP	—/2 mo	AS(L-C,V)-IM-N,El/CE	K	Dawson & Nabarro (1953)
111 ↕ 114	*3 ↕ *7	N.D.	—/RD,CF(4)	N.D.	AS(L-C)-IM,N,El/CE(4)	K	Cochrane & Bowden (1954)
115 ↕ 129	*1	T(1),Familial (2)	LBW(4)/S(1)	+(4)/	Ao-St(1)/En-F,Th(13)	K(2)	Kelly & Andersen (1955)
		I(4),MB(6)	↓O_2(3)/↓O_2(4);RD(5);ECG(1);Thr(3);↑L(1)	12 hr ↕ 8 d	Anom. C(1)/Va(2)-St		
	*30	FP(3),SA(5)	—/CF(11);CE(10)				
130	*9	N.D.	—/RD,CF(term.)	+/3 d	AS(L-C,V),IM,El,Ca/MI-Mas	N.D.	Leach (1955)
131	*4	N.D.	—/An,V;CF;↑CR	N.D.	AS(L-C)-IM,N,El;Ao,G/CE	K	Zischka (1955)
132	*5	N.D.	—/RD,An,V,T	+/2 d	AS(L-C)/MI-Mas,N;En-F,Pl	N.D.	Martelle (1955)
133	*15	N.D.	—/An,V,C,CF	N.D.	AS(G)/M,SubEn-F;Va-St	N.D.	Hallman (1955)
134	*10	N.D.	N.D.	N.D.	—/M-Ca;En-F,Th	N.D.	Ahvenainen & Hjelt (1956)
135	*3	N.D.	↓O_2,C/—	N.D.	—/M-N	B,K	Ahvenainen & Hjelt (1956)
136	*10	N.D.	—/An,V,CLe,P;↑Ca,↑L	N.D.	AS(L-C,Ce)Thr/M-Dis	B,K	K. Rhany & Mitchell (1956)
137	*26	N.D.	—/An,V,C,Le,GF,MR	N.D.	AS(L-C)IM,Ca/M-Ca,Va-St	B,K	Schlessinger *et al.* (1956)
138	*24	N.D.	—/↓O_2(sudden)	+/5 hr	AS(Sm,L-C)-IM/M-Dis-N	N.D.	Traisman (1956)
139	*2	N.D.	—/↓O_2(sudden);CF(term.)	+/2 wk	AS(L-C)-N,El,Ca/M-Dis-N	N.D.	Thomas *et al.* (1956)
140	*3	N.D.	—/RD(sudden)	+/12 hr	AS(L-C,V)-IM,Ca,N,El/SubEn,M-Mas,N;CE	N.D.	Thomas *et al.* (1956)

141	*30	N.D.	N.D.	N.D.	—/MI-Mas,En-F,Th;CE	N.D.	Thomas *et al.* (1956)
142	*16	N.D.	LBW/GF, ↑ BP	N.D.	AS(Sm,L-C,V,G)IM,N,El/—	K	Weens & Marin (1956)
143	*2	N.D.	—/ ↓ O_2,RD(sudden)	+/—	—/M-N(Dis),F,Ca;En-F,Th	N.D.	Hamne & Ranstrom (1957)
144	*6	N.D.	N.D.	N.D.	—/M-Dis;En-F,Th	N.D.	Hamne & Ranstrom (1957)
145	*1	FP Familial—sibs	—/ ↓ O_2,RD,P	+/4 d	AS(Sm,L-C,V);IM-N,El,L/CE;M-Dis	N.D.	Hunt (1957)
146	*1	FP	—/ ↓ O_2,RD,P	+/4 d	AS(L-C,V)/MI-Mas,Ca;CE	N.D.	Hunt (1957)
147	**17	N.D.	LBW/ ↑ Ca, ↑ L	N.D.	Living at report	B	Daeschner & Daeschner (1957)
148	**18	N.D.	LBW/GF,F, ↑ Ca, ↑ BP	N.D.	Living at report	B,K	Snyder (1958)
149	*5	N.D.	—/Co,Le,GF,F,CF; ↑ CR, ↑ BP, ↑ L, ↑ Ca	N.D.	Ao;AS(G)IM,Thr/Va;CE	B,K	Joseph & Parratt (1958)
150	*10	N.D.	—/GF, ↑ CR,ECG-MI	—/3 mo	AS(Sm,L-C,G);IM-N,El,Ca/—	N.D.	Gelderen *et al.* (1959)
151	*6	N.D.	LBW(6)/An,V(6);Le(6);Tr(2)	N.D.	AS(G)(6)/—	K(1)	Lefebvre (1959)
↕	↕	N.D.	—/MR(5);F(1)	N.D.	IM,L(6)/—	N.D.	
156	*19	N.D.	—/ ↑ Ca(6)	N.D.	N.D.	N.D.	
157	*14	N.D.	—RD,MR,F, ↑ BP;CF	N.D.	N.D.	B,K	Illig & Prader (1959)
158	**19	(SA)	—/RD,Tr,CF,ECG;(MI)	N.D.	—/Va-St(Surg. repair) Living at report	N.D.	Sissman *et al.* (1959)
159	**24	N.D.	↓ O_2,C/C,Le, Tr; ↑ BP,Ca, ↑ L	N.D.	Living at report	B,K	Amann (1959)
160	*>1	(SA),FP Familial—sibs	—/ ↓ O_2,RD, ↑ CR(sudden)	+/2 d	AS(Sm,L-C,Pu,V,G);IM,N,El,Ca/CE,M-N,En-F,Pl	N.D.	Moran & Becker (1959)
161	*2	(SA),FP	—/ ↓ O_2	+/5 hr	AS(G)-IM,N,El,Ca/—	N.D.	Moran & Becker (1959)
162	*2	FP	—/RD(sudden)	+/1 d	AS(Sm-C,Pu);IM,Ca,F/SubEn-N	K	Chipman (1960)
163	**11	N.D.	—/GF(4);MR(4);F(4); ↑ Ca(4)	N.D.	Living at report	B(2)	O'Brien *et al.* (1960)
↕	↕						
166	**18	N.D.	—/Tr(2);Le(1); ↑ BP(1); ↑ L(3)	N.D.	N.D.	N.D.	
167	*5	FP	—/RD,An,V,CF(term); ↓ CR,ECG	N.D.	—/En-F,Th	N.D.	Winter *et al.* (1960)
168	*2	FP	—/RD,An,V,Tr,CF; ↓ CR,ECG	N.D.	—/En-F,Th	N.D.	Winter *et al.* (1960)
169	*5	N.D.	(Intest. resect.)	N.D.	AS(Sm-C,V);IM-N,El,Ca/CE;En-F,Th	N.D.	Nielsen (1961)
170	*2	N.D.	N.D.	N.D.	AS(Sm-C,V);IM-N,Ca,El/—	N.D.	Nielsen (1961)
171	*19	N.D.	—/An,V,C,GF,CF,CE;Thr, ↑ BP, ↑ Ca	+/—	AS(Sm-C)-IM/Va-St	N.D.	Rashkind (1961)
172	*2	N.D.	—/ ↓ O_2,RD,An,V;CF(term.)	+/3 d	AS(Sm-C,V)-Ca,Thr/—	K	Bodner (1961)
173	*11	N.D.	—/S, ↑ CR,ECG(MI)	—/1 mo	AS(Sm-C)IM,Ca/MI-Mas,N,Ca;En-F,Th	N.D.	Weber *et al.* (1962)
174	*<2	N.D.	N.D.	+/6 d	—/MI-Mas,N,F	N.D.	Coleman & MacDonald (1962)
175	*2	FP	—/ ↓ O_2,RD,V,shrieks(sudden)	+/2 d	AS(Sm,L-C)/M-N(Dis),CE	N.D.	Gower & Pinkerton (1963)
176	*2	FP	—/ ↓ O_2,RD,V,P(sudden)	+/<1 d	AS(Sm,L-C)/M-N(Dis),CE	N.D.	Gower & Pinkerton (1963)

(*continued*)

TABLE A-6A. (*Continued*)

Case No.	Age (mo)[a]	Gestational factors (maternal or fetal)[b]	Infantile findings (neonatal/later infancy[c])	SD/TI[d]	Pathologic findings (arterial/cardiac)[e]	ABN[f]	Reference
177	*<2	N.D.	—/↓O_2,RD,P,↑CR(sudden)	+/1 hr	AS(L-C,Pu)-IM,N,El,Ca/—	K	Bickel & Janssen (1963)
178	*8	N.D.	—/↓O_2,RD(5th wk);CE,CF,ECG	N.D.	AS(Sm,L-C,Pu,V);IM-Ca/M-Dis;En-F,Th	K	Bickel & Janssen (1963)
179	*4	PA	—/V,An,C,F,↑Ca,↑L	+/—	AS(Sm-C,V,G/M-Ca	B	Wilkerson (1964)
180 ↕ 182	**<1 **<2	N.D. N.D.	—/S,D(3),ECG N.D.	N.D. N.D.	Living at report N.D.	N.D. N.D.	Fraser *et al.* (1964)
183	*5	FP	—/GF,S	N.D.	—/CE,M-L(Dis)	N.D.	Sacrez *et al.* (1964)
184	*<2	FP	LBW/GF,MR,F	N.D.	AS(Ce);Ao-At	N.D.	Williamson (1964)
185	*<2	Familial—sibs	—/Ir,P,Shrieks (sudden)	+/1 d	AS(Sm,L-C),IM-N,El,F/CE	N.D.	Meurman *et al.* (1965)
186	*2	N.D.	C,↓O_2/—	N.D.	AS(Sm-C)IM,Thr;Ao-St/M-F(Dis):En-F,Th	N.D.	Oppenheimer & Esterly (1966)
187	*3	N.D.	—/S,D,ECG	N.D.	Living at report	N.D.	Jervell *et al.* (1966)
188	*24	N.D.	—/S,D,ECG	N.D.	Living at report	N.D.	Lacker & Finkelstein (1966)
189	*9	N.D.	—/GF,MR,F,CF(1 mo);↑Ca,↑L	N.D.	(Pu-St)	N.D.	Cornell *et al.* (1969) Garcia (1964)
190	*<2	N.D.	—/RD,ECG(sudden)	+/2 d	AS(Sm,L-C,Pu,Ce);IM-N,El,Ca/SubEn-N,F	N.D.	Perreault *et al.* (1966)
191	*12	N.D.	N.D.	N.D.	AS(G)-L,Pl/M-F(Dis),En-F,Th	N.D.	Oppenheimer & Esterly (1967b)
192	*18	N.D.	N.D.	N.D.	AS(G)IM/M-F(Dis)	N.D.	Oppenheimer & Esterly (1967b)
193	*4	N.D.	N.D.	N.D.	AS(L-C,V,G)-IM/M-F(Dis)	N.D.	Oppenheimer & Esterly (1967b)
195	*3	N.D.	N.D.	+/—	L-C Thr/(Mitral veget)	N.D.	Oppenheimer & Esterly (1967a)
196	*3	N.D.	N.D.	+/—	L-C Thr/(Mural)	N.D.	Oppenheimer & Esterly (1967a)
197	*7	N.D.	—/Myocarditis	+/<1 hr	L-C Thr/(Mural)	N.D.	Oppenheimer & Esterly (1967a)
198	*12	N.D.	—/Myocarditis	+/1 hr	L-C Thr/(Mural)	N.D.	Oppenheimer & Esterly (1967a)
199	*24	N.D.	—/↑BP	N.D.	AS-C,Thr/—	K	Oppenheimer & Esterly (1967a)

200	*30	N.D.	—/↓O_2,RD;shrieks;CE,↑CR,ECG	N.D.	AS(Sm,L-C)IM/CE,M-F(Dis);Thr,S(MI)	N.D.	Holm (1967)
201	*14	N.D.	—/Ap(13 mo),ECG;S(last mo)	—/1 mo	AS(Sm,L-C);IM-N,El,Ca/MI-Mas,Dis;S(Conduct. abn.)	N.D.	Lev *et al.* (1967)
202	**21*	N.D.	—/S,D,ECG	N.D.	Living at report	N.D.	Lamy *et al.* (1967)
203	**12	N.D.	—/S,D,ECG	N.D.	Living at report	N.D.	Jervell & Silverstein (1967)
204	**<2	N.D.	—/↓O_2,CF	N.D.	AS(L-C)-IM;Pu-St/MI(Dis)	N.D.	Macmahon & Dickinson (1967)
205	*18	FP	—/Tr,P,↑CR(sudden)	—/6 wk	—/M-L,En-F,Pl	N.D.	Ross & Belton (1968)
206	*13	N.D.	N.D.	+/—	—/SubEn-N;En-F,Pl,S(Conduct. abn.)	N.D.	Reid *et al.* (1968)
207	*16	N.D.	—/↑CR,ECG,Thr(sudden)	+/3 d	AS(V,G)-L/M-Mas,Dis,N	N.D.	Reid *et al.* (1968)
208 ↕ 217	**2 ↕ *30	N.D.	—/↓O_2(4);RD(7);S(2);P(1);Thr(1)	+(4)/<1 d 1 mo	AS(L-C)(3);Sm-C(1)/M(5)-Mas(2),F(4)Pu(2);IM(1);L(1);Thr(2)/N(2);Va(2)	N.D.	Bor (1969)
218	*<3	FP,Familial —sibs	Gastric surg.	+/—	AS(Pu,Ao,C)-IM/M-N,F(Dis)	N.D.	McDonald *et al.* (1969)
219	**9	FP,Familial —sibs	—/CE,Pu-At	N.D.	Living at report	N.D.	McDonald *et al.* (1969)
220	**<1	FP,Familial —sibs	—/CF,Pu-At,Va	N.D.	Living at report	N.D.	McDonald *et al.* (1969)
221 ↕ 231	*<1 ↕ *9	N.D.	—/ECG(MI)(6);Thr(1)	N.D.	—/M-N(1);Pa(10);SubEn-N(3);Va(2);En-F,Th(2)	N.D.	Kangos *et al.* (1969)
232	*5	N.D.	—/An,V,Le,ECG,Thr	—/1+ mo	AS(Sm,L-C,V,G),IM,Thr/—	N.D.	Witzelben (1970)
233	*5	MB,FP	—/V,Le,ECG,Thr	—/11 d	AS(Pu)-IM,N/En-F,Th	N.D.	Raphael *et al.* (1970)
234	*3	MB	—/RD(sudden	+/—	AS(L-C,Pu,V)/IM,Ca	N.D.	Raphael *et al.* (1970)
235	*5+	FP	—/C	N.D.	AS(G)-Ca/M-N	K	Vainsel (1970)
236	**18	N.D	—/S,D,ECG	N.D.	Living at report	N.D.	Olley & Frank (1970)
237	**18	N.D.	—/S,D,ECG	N.D.	Living at report	N.D.	Olley & Frank (1970)
238	*6	N.D.	—/RD	N.D.	—/M(Ultramicr. abn.)	N.D.	Hug & Schubert (1970)
239	*13	FP(SA)	—/V,Le,S(sudden)	—/5 d	—/M,SubEn-MI(Mas)-L	K	MacMahon (1971)
240	*1	N.D.	LBW/CE	N.D.	N.D.	B	Griscom (1971)
241	*2	FD,ECG	CF/—	N.D.	—/En-F,Th;S(Conduct. abn)	N.D.	R. Miller (1972)
242	*13	N.D.	—/CF	—/2 mo	—/M,En-F,Th	N.D.	Martinez-Hernandez *et al.* (1972)
243	*<3	N.D.	—/ECG(MI)	N.D.	Ao-At/M-N,Ca	N.D.	Lin (1972)
244	*16	N.D.	—/RD,↑CR,ECG(sudden)	N.D.	—/M-N(Dis)	N.D.	Haese (1972)
245	*16	N.D.	—/CF,↑CR,ECG(sudden)	—/3 d	—/M-L;Ultramicr. abn.	N.D.	Bove & Schwartz (1973)
246 ↕ 251	*3 ↕ *19	N.D.	N.D.	N.D.	—/En-F,Th;Va-St S:(Conduct. abn.)	N.D.	Elliot & Elliot (1973)
252	*<2	N.D.	LBW/ECG,CF;↑CR,↑BP	N.D.	AS(L,Sm-C,V,Pu-M,Ca,El/Ce	B (joints)	Meradji *et el.* (1978)
253	**24	N.D.	RD,CF/ECG,AS(G)-X-ray	N.D.	Living	N.D.	Meradji *et al.* (1978)

TABLE A-6B. Infantile Ischemic Heart Disease: > 1 Month to 2½ Years

Number	Category	Other abnormalities; symptoms	Number surveyed; category[b]	Investigator(s)
22	Arteriosclerosis	Nephrosclerosis	80 infants and children with nephrosclerosis	Mitchell (1930)[a]
(20)	Cardiomegaly (14: sudden death)	Symptoms: Preterminal cramps, syncope, weakness, vomiting, edema		Stoloff (1928)[a]
52	Arteriosclerosis: medium coronaries Perivascular myocardial fibrosis	Sudden death after syncope		Kugel and Stoloff (1933)b[a]
74	Endocardial fibroelastosis (EFE); murmurs; cardiomegaly (94 %); ECG abnormality; block	No other cardiac anomaly Convulsions: occasional		Blumberg and Lyon (1952)[a]
24	EFE; coronary calcification; MI			Thomas *et al.* (1956)[a]
< 500	EFE (150); major coronary disease (280, incl. anomalies); paroxysmal atrial tachycardia (PAT)(28); hypertension (50)		1580 with infantile heart failure (1–12 mo)	Keith (1956)[a]
			About ⅓ of 150 with hypertension (6–12 mo)	
30	Arteriosclerosis: coronaries (thick intimomedia)		1 mo to 1 yr of age	Schornagel (1956)
< 50	Arteriosclerosis: elastica degeneration first; then intimal thickening; fat infiltration		< 3 yr of age	Moon (1957)
< 640	Congenital heart block; tachycardia; hypertension	Hypertelorism: cardiofacies (5 % familial)	1250 with congenital heart disease (40 % outflow obstruction: all with hypertension)	Wood *et al.* (1958)[a]
24	Coronary calcification; ECG abnormality	Hypercalcemia; 1 with renal acidosis; 1 with osteogenesis imperfecta	Hypercalcemic infants: 1 month to 1 year	Coleman (1959)
56	Outflow obstruction: left; right (stenoses, hypoplasia of major, peripheral vessels) Medial thickening; luminal narrowing; murmur	Hypercalcemia: occasional; cardiofacies in > half Growth, mental retardation in half; aged appearance occasional; calcinosis: kidneys < half; labyrinth: occ. dental abnormalities common; familial in 19 of 56	Categorization by single or combined cardiovascular lesions; time of symptoms; death (correlation with high im dosage vitamin D)	Beuren *et al.* (1962, 1964, 1966) Jorgensen and Beuren (1965)[a]

47	EFE (usually with aortic outflow obstruction) (8 with heart block or A-V dissociation; 4 with fibrillation)	Symptoms in first year in 17		Moller *et al.* (1964)
< 104	Outflow obstruction (supravalvular aortic: 8; aortic valvular: 74; suboartic: 24) Peripheral pulmonary stenosis common	Mental retardation; cardiofacies common	Survey of outflow obstruction in 1 medical center and literature review Categorization of lesions	Peterson *et al.* (1965)
18	Coronary arteriosclerosis: small arteries, MI		153 < 1 month to 1 year (12% when sought)	Blanc *et. al.*(1966)
< 96	Early myocardial damage (stain technic)		135 infants and young children	Berry (1967)[a]
68	Aortic coarctation; hypertension (4 with MI)		148: < 2 years with hypertension	Oppenheimer and Esterly (1967)
40	Arteriosclerosis: intimomedial thickening		Comparison Ashkenazim, Yemenite, Bedouin infants, children	Neufeld and Vlodaver (1968)
78	Aortic coarctation		Infants up to 6 months	Sinha *et al.* (1969)[a]
< 12	EFE; tricuspid stenosis Arteriosclerosis: thickened coronary intima		6: 1 day to 6 months 9: stillborn to 16 months	Bryan and Oppenheimer, (1969)
< 59	PAT; W-P-W- syndrome in 9		Infants and children	Simcha and Bonham-Carter (1971)
(<35)	Gross calcification of *iliac* arteries		11 infants 1–11 months; 28 of 1–12 years	Meyer and Lind b)1972)[a]
(5)	Gross Calcification of *carotid siphon*		5 infants 1–2 years	Meyer and Lind (1972)[a]
<25	Subaortic stenosis	Surgical correction	26-year study	Kelly *et al.* (19 2)[a]
<51	Subaortic stenosis; ECG abnormal; W-P-W in 4	Surgical correction	40 infants and children	Newfeld *et al.* (1976)[a]
<586	Congenital heart disease	Surgical correction; 90% mortality (late mortality after surgery: arrhythmias)	2365 in 9-year study in 1 medical center ¼ autopsies in children show heart disease	Van Praagh, M Visner (1976)[a]

[a]Reference listed in Table A-7.
[b]< indicates that the number is not limited to infants 1 month to 2½ years.

TABLE A-7. Sources of Cases in Infantile Ischemic Heart Disease, Cited in Tables A-5A,B and A-6A,B

Reference	Table No.	Case Nos.
Ahvenainen EK, Hjelt L: *Ann Paediat Fenn* **1**:12–26, 1956.	5A	67–74
	6A	134,135
Amann L: *Mschr Kinderh* **107**:5–13, 1959.	6A	159
Andersen DH, Schlesinger ER: *Am J Dis Child* **63**:102–125, 1942.	6A	32,33
Andersen SR: *Acta Path Microbiol Scand* **22**:180–187, 1945.	5A	31
Bacon JF: *JAMA* **188**:933–935, 1964.	5A	109
Baggenstoss AHM Keith HM: *J Pediat* **18**:95–102, 1941.	6A	29
Bellet S, Gouley BA: *Am J Med Sci* **185**:458–465, 1932.	5A	17
Berry CL: *J Clin Path* **20**:38–41, 1967.	6B	
Beuren AJ, Apitz, Harmjanz D: *Circulation* **26**:1235–1239, 1962.	6B	
Beuren AJ, Apitz J, Stoermer J, Kaiser B, Schlanger H, Berg W, Jorgensen G: *Mschr Kinderh* **114**:457–470, 1966.	6B	
Beuren AJ, Schulze C, Eberle P, Harmanj D, Apitz J: *Am J Cardiol* **13**:471–483, 1964.	6B	
Bickel E, Janssen W: *Arch Kinderh* **169**:274–285, 1963.	6A	177, 178
Blanc WA, Franciosi RA, Cadotte M: *Med Hyg* **24**:216–220, 1966.	5A	112, 113
Blumberg RW, Lyon RA: *Am J Dis Child* **84**:291–308, 1952.	5A	53,54
	6A	79–99
	6B	
Bodner E: *Franfurt Zschr Path* **71**:657–676, 1961–1962.	6A	172
Boldero JL: *Brit J Radiol* **24**:43–45, 1951.	6A	78
Bor I: *Arcg Dis Childh* **44**:268–281, 1969.	5A	147–149
	6A	208–217
Bove KE, Schwartz DC: *Arch Path* **95**:26–36, 1973.	6A	245
Caldera R, Ramette I, Rossier A: *Ann Pediat* **22**:593–597, 1975.	5B	
Chipman CD: *Canad MAJ* **83**:955–957, 1960.	6A	162
Clapp JE, Naeye RL: *JAMA* **178**:1039–1040, 1961.	5A	78
Clifford SH: *J Pediat* **18**:567–578, 1941.	5B	
Cochrane WA, Bowden DH: *Pediatrics* **14**:222–231, 1954.	5A	56–61
	6A	111–114
Coleman EN: *Brit Med J* **2**:467–470, 1959.	6B	
Coleman EN, MacDonald AM: *Arch Dis Childh* **37**:444–447, 1962.	5A	110
	6A	174
Cornell WP, Elkins RC, Criley MJ, Sabiston DC: *J Thõr Cardiovasc Surg* **51**:484–492, 1966.	6A	189
Cosgrove G, Kaump D: *Am J Clin Path* **16**:322–340, 1946.	5A	32–34
	6A	38–40
Craig JM: *Bull Intl AM Museums* **30**:15–67, 1949.	5A	39–49
	5B	
	6A	51–70
Crawford BL, Weiss E: *J Tech Meth* **12**:180–183, 1929.	6A	8
Creery RDG: *Lancet* **2**:17–19, 1953.	6A	108
Daeschner GL, Daeschner CW: *Pediatrics* **19**:362–371, 1957.	6A	147
Dawson IMP, Nabarro S: *J Path Bact* **66**:493–498, 1953.	6A	110
Diamond M: *Arch Path :137–145, 1932.*	5A	18
Dock W: *JAMA* **131**:875–878, 1946.	5B	
Durant G: *Bull Soc Anat Paris* **74**:97–101, 1899.	5A	1
Elliot GB, Elliot JDA: *Arch Path* **95**:321–324, 1973.	5A	156, 157
	6A	246–251
Esterly JR, Oppenheimer EH: *Bull Johns Hopkins Hosp* **119**:191–199, 1966.	5A	118–142

(*continued*)

TABLE A-7. (*Continued*)

Reference	Table No.	Case Nos.
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Fangman RJ, Hellwig CA: *Am J Path* **23**:901–902, 1947.	5B	
Farber S, Hubbard J: *Am J Med Sci* **186**:705–713, 1933.	5A	19,20
	6A	14–19,23
Field MH: *Arch Path* **42**:607–618, 1946.	6A	36
Franciosi RA, Blanc WA: *J Pediat* **73**:309–319, 1968.	5A	111
Fraser GR, Frogatt, P, James TN: *Quart J Med* **33**:361–384, 1964.	6A	180–182
Ganeff N: Inaug dissert, 1910 (cited by Cosgrove & Kaump)	5A	8
Garcia RE, Friedman WF, Kaback MM, Rowe RD: *New Eng J Med* **271**:117–120, 1964.	6A	189
Gault MH, Usher R: *New Eng J Med* **263**:379–382, 1960.	5A	77
Gelderen HH, Gemund JJ, Arkenbout PM: *Kindergeneesk* **27**:63–69, 1959.	6A	150
Gore I, Arons W: *Arch Path* **48**:1–12, 1949.	6A	50
Gower ND, Pinkerton JRH: *Arch Dis Childh* **38**:408–411, 1963.	6A	175–176
Griscom NT, Craig, JN, Neuhauser EBD: *Pediatrics* **48**:883–895, 1971.	6A	240
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