Magnesium Requirements in Human Nutrition

By *M. S. Seelig*

Department of Medicine, Goldwater Memorial Hospital, New York University Medical Center, New York, USA

Zusammenfassung

Der Bedarf an Magnesium wird unterschätzt. Dies hat die folgenden Gründe: (1) Es besteht die falsche Auffassung, daß der tägliche Bedarf die Menge ist, die Zeichen und Symptome schweren Mg-Mangels oder Hypomagnesämie vermeidet; (2) Schwierigkeiten bei der Bestimmung des zellulären Mg; Plasma-Mg ist ein schlechter Indikator für den Mg-Status; (3) Die Magnesium-Bilanz wird aufrechterhalten bei suboptimalen Aufnahmen und Gewebekonzentrationen; (4) Der Bedarf ist gesteigert im Wachstum, während Reparaturvorgängen, Streß, Diätimbalanzen und durch Umweltfaktoren. Mg-Mangel verursacht viele Anomilitäten; sogar parenteral appliziertes Mg ist im allgemeinen sicher.
Schlußfolgerung: Bevor keine endgültigen Daten vorliegen über die optimale Aufnahme unter physiologischen und pathophysiologischen Bedingungen, sollte die Mg-Aufnahme für junge Erwachsene auf 6 bis 10 mg/kg/Tag erhöht werden und um den doppelten Betrag bei aktiven Anabolismus und/oder unter Streßbedingungen.

Summary

Magnesium requirements are underestimated. This is due to:(1) the misconception that the daily requirement is the amount that prevents signs and symptoms of severe deficiency or hypomagnesemia; (2) the difficulties in assaying cellular Mg, plasma Mg being a poor index of body status; (3) the maintenance of Mg-balance at suboptimal intakes and tissue levels; and (4) the increased needs caused by growth, development, repair, stress, dietary imbalances, and environmental factors. Mg deficiency causes many abnormalities; even parenteral Mg is generally safe. Thus, until definitive data are available as to optimal intakes under different physiologic and pathologic conditions, Mg-intakes should be increased to 6—10 mg/kg/day for young adults, and to twice that much for those undergoing active anabolism, or under stress.

Résumé

Les besoins en Mg sont sous-estimés. Ceci est dû:
1) à la conception erronée selon laquelle le besoin quotidien est la quantité qui prévient les signes et les symptomes du déficit magnésique grave et de l'hypomagnésémie,
2) aux difficultés dans l'évaluation du Mg cellulaire, le Mg plasmatique étant un mauvais indice des taux tissulaires,
3) à la capacité de l'organisme de maintenir l'équilibre du Mg pour des administrations et des taux tissulaires suboptimaux et
4) aux besoins accrus créés par la croissance, le développement la réparation, le stress, les déséquilibres alimentaires, et les facteurs génétiques et de l'environnement.
Le déficit magnésique provoque plusieurs anomalies dans la structure et le fonctionnement. Par contre, le Mg est remarquablement inoffensif même lorsqu'il est administré par voie parentérale, à condition qu'il n'existe pas d'insuffisance rénale, et qu'il ne soit pas administré rapidement par voie intraveineuse.
Ainsi, jusqu'à ce que des données définitives soient disponibles pour les administrations optimales dans différentes conditions physiologiques et pathologiques, les administrations *per os* devraient être accrues jusqu'à 6—10 mg/kg/jour pour les adultes jeunes, et à deux fois plus pour les sujets subissant un anabolisme actif, ou pour ceux se trouvant sous l'effet d'un stress.

Introduction

Controversy and confusion still attend consideration of human magnesium (Mg) requirements. Ten years after the First International Symposium on Magnesium, it is necessary to repeat, "The place of Mg deficit in medicine is still not universally accepted [269]. Magnesium is not unique in having its requirements for maintenance of optimal growth, development, and health poorly appreciated. Most to blame for physicians' reluctance to accept the possibility that Mg deficiency might be contributory to medical problems, is the classic concept that the daily requirement of a nutrient is the amount that prevents overt signs and symptoms of deficiency. In the case of Mg, plasma levels are maintained within fairly narrow limits, despite losses and needs that exceed supplies or absorptive and retention-capacities. Hypomagnesemia, sufficient to cause convulsions or dysrhythmias that are refractory to therapy other than Mg, reflects depletion rather than deficiency. Yet even in such instances, most clinicians attribute the efficacy of Mg-therapy to its pharmacologic activity, rather than to repair of a deficiency.
Lesser degrees of deficiency are recognized predominantly by those who have demonstrated reduced erythrocyte Mg-levels and Mg-responsiveness of patients with a variety of neuromuscular or psychoneurotic syndromes [69, 70, 72, 74, 87, 88, 137, 138]. Metabolic balance studies have supported the contention that in such patients, Mg-intakes from their self-selected diets are inadequate to maintain Mg-balance [69, 73, 74]. With few exceptions [87, 88, 138, 139, 277] except in Latin-language countries, most physicians do not accept the likelihood of marginal Mg-deficiency in neuromuscular or psychological disturbances, in disorders of the alimentary tract or endocrine system or as a possibly contributory factor to the early origins, or early or later manifestations of cardiovascular, renal, skeletal or immunologic diseases.
Marginally low plasma Mg levels, that might reflect more significant tissue deficiency, are usually disregarded. Difficulties in determining and interpreting cellular levels limit attempts to obtain tissue Mg levels. Only in research ventures are tissue Mg levels measured. Further confounding the problem is the complexity of interactions that affect dietary Mg-requirements. The metabolic balance technic provides the baseline requirements data, usually as influenced by single dietary variants under strictly controlled conditions. Invaluable as a method of determining minimum requirements in a test environment, this procedure is not readily

adaptable to usual living conditions, because of the multiplicitiy of factors that affect requirements.
A 1964 analysis [275], of metabolic balance data collected from studies done throughout the world, indicated that Mg-intakes by adults, of less than 5 mg/kg/day, are unlikely to maintain Mg equilibrium. Intakes of 7—10 mg/kg/day, particularly by young men, are probably preferable [269]. After study of factors that increase requirements, and consideration of the safety of orally administered Mg to those without significant impairment of renal clearance, the author reiterates that recommendation. Translating this to total daily Mg intakes, 450—700 mg might be desirable for a 70 kg man, and as much as 600—1000 mg/day for a 100 kg man — whether much of his weight is fat or muscle. Young women maintain equilibrium on lower mg/kg/day Mg-intakes [269].
Basing their recommendations largely on metabolic balance studies, much lower intakes were recently officially recommended in the United States [101]: 300 and 350 mg/day for young women and men, respectively; 400 mg for 15—18 year old boys; 450 mg for pregnant or lactating women. The low infant RDA (Recommended Dietary Allowance) for Mg (70 mg/day, or less than 10 mg/kg/day), based on the amount present in infant formulas [101, 307] urgently requires re-evaluation, in view of clinical evidence of infantile hypomagnesemia — especially in bottle-fed babies (Review: [271]), and early metabolic balance studies that rapidly growing children sustain strongly positive Mg-balance while on diets providing as much as 20 mg/kg/day or more *(infra vide)*. This evidence, that high Mg-intakes result in retention of large amounts of Mg by subjects undergoing growth and repair, suggests that the optimal Mg-intakes of pregnant and lactating women, adolescents, athletes — in-training and in competition, and convalescents, be fully studied.
That even the modest, officially recommended, Mg-intakes are not met by most Americans and Canadians, has been shown by dietary surveys [200, 292, 307, 324, 330]. Analysis of thousands of typical sample meals of American children and adults of all ages and both sexes, showed Mg-intakes to be below the RDA. Most of randomly selected students in 50 colleges in the United States [307] and one from Canada [292] chose meals that provided much less than the RDAs for Mg and twice as much, or more, calcium (Ca) and phosphorus (P) (Figure 1). This dietary pattern causes concern when considering the straightline correlation of the increased incidence of ischemic heart disease death rates in countries with high dietary Ca/Mg ratios [158, 311], and the evidence that high P-intakes intensify damage caused by Mg-deficiency [272, 272]. Other diseases, notably gastrointestinal neoplasms and leukemias, have geographic differences in distribution that match low Mg-availability [7, 270]. Animal and *in vitro* studies provide data that suggest contributory roles of high Ca/Mg ratios [12, 13, 270].

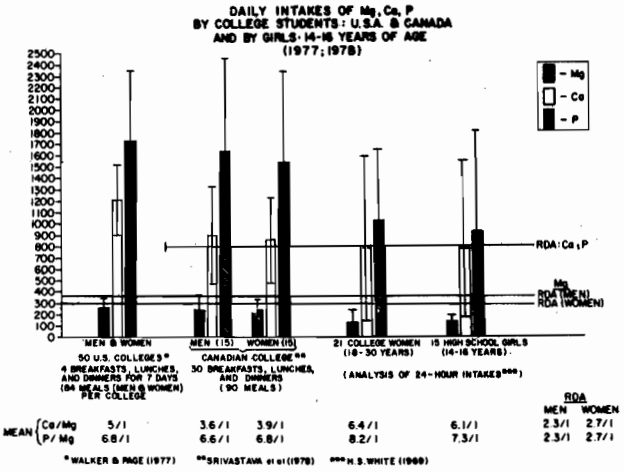

Fig. 1

Intervention studies are being implemented or planned in Canada [336], and Finland, to determine whether Mg supplements, given to high-risk individuals or population groups will reduce the incidence of cardiovascular diseases (personal communications: *J. Marier, H. Karppanen*). We should also ascertain whether, and to what extent, Mg-supplementation of infants would prevent Mg-responsive infantile irritability and convulsions, to which high-risk infants and formula-fed infants are more vulnerable than are breast-fed normal infants [267, 271, 274]. Whether such supplements can reduce the incidence and severity of deseases with early and late manifestations resembling those producible by experimental Mg deficiency, the roots of which might be in early life [268, 271, 272], will require much more investigation and evaluation. Whether Mg supplements might protect against cardiovascular consequences of diets too rich in protein, fat, and sugar, and in Ca, vitamin D, Na and P will remain speculative until long-term intervention studies can be extended and evaluated. In view of fiber's reduction of retention of Mg and trace minerals, evaluation of Mg requirements should be part of this approach to preventive medicine.

Difficulties in establishing human magnesium needs

Factors that affect human nutrient requirements

There are individual, dietary, and environmental factors that influence the amount of each essential nutrient that is needed to maintain resistance to disease and optimal physical fitness. [143, 337]. Under essentially normal conditions, in the developed world, the host factors are the most important. Individual differences: age, sex, genetic factors, activity, customs, and responses to infection and other stresses, all affect nutritional requirements. Dietary factors: chemical form and

quantity of the nutrient, levels of other nutrients, and food processing influence the amount available to the consumer. Environmental factors, such as water and soil, climate, season and altitude, and stress factors, all influence either the availability or the retention of the nutrient.

Interactions among all of these factors influence nutritional requirements of individuals, families, racial, or ethnic groups and of these groups in different geographic areas. Epidemiologic surveys, that correlate at least some of the nutritional variants with differences in disease distribution patterns, provide clues to the role nutrition can play in predisposing to, or protecting against, pathologic processes. Intervention studies, in which we change the intake of one or more nutrients that are suspected of playing a role and evaluate subsequent changes in morbidity and mortality of high risk-groups, provide further insight into the efficacy of altering the nutrient-intake.

Interaction of factors that affect magnesium requirements (Figure 2)

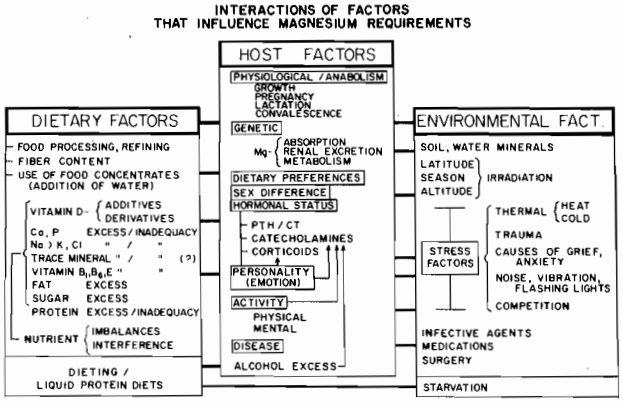

Fig. 2

Since Mg plays such an important role in protein and nucleic acid synthesis [79, 253, 310, 318, 321, 322, 341] it is to be expected that those undergoing rapid growth and repair have high Mg-requirements. Primary Mg-malabsorption [222, 227, 228, 257, 294] and renal-wastage [104, 110, 209, 229, 237, 255], often familial, indicate that there are genetic differences in Mg-requirements. These abnormalitites are probably at the ends of bell-shaped curves of distribution of Mg-absorptive and renal-retention capacities. The extent to which Mg requirements are affected by genetic differences in utilizing nutrients (e. g., Ca, Zn, or vitamins D, B_1, B_6, E, and A) must be investigated. Of particular interest are susceptibilities and dependence on nutrients — excesses or deficiencies of which affect Mg-utilization. Whether one is phlegmatic or exitable is at least partially genetically determined, although environmental factors play a role. One's physical and mental prowess, in conjunction with one's competitiveness (to which genetics and environment contribute), will influence the degree to which one seeks the stress of excessive physical training and athletic competition, or intellectual or business ventures that create psychological strains, and can lead to overwork. Those whose work or preference subjects them to crowding, and to noise, vibration and flickering lights as in subways or discoteques — are also subjected to stress and the release of the stress hormones: catecholamines and corticosteroids. These hormones have long been known to mediate both physiologic and pathologic responses to stress [17, 235, 236, 281, 283, 284]. Cardiac and renal damage is intensified by Na, P, Ca, and calcemic agents. Potassium, Cl, and Mg-inadequacy each worsens the lesions; the administration of each is protective [17, 169, 171, 244—247, 281—284, 300, 301]. Less widely appreciated is the increase in secretion or release of corticoids that is caused by low Mg [41]. Catecholamine release is also increased by low Mg and high Ca concentrations [30, 62, 236, 254]. Some of the pathways by which stress causes Mg loss, and the conditioning to such loss by dietary imbalances, are designated in Figure 3.

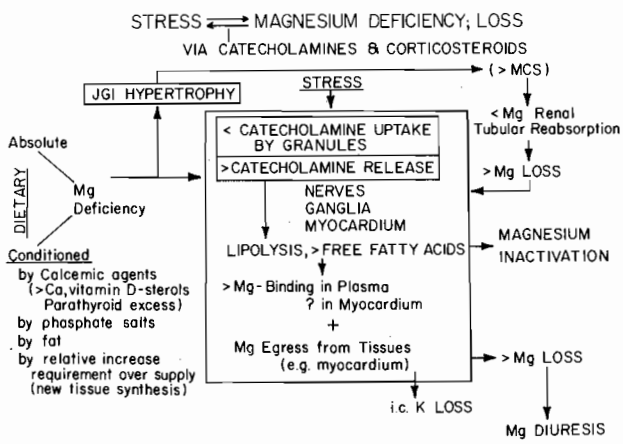

Fig. 3

Metabolic balance estimation of nutrient requirements

A valuable investigative tool, metabolic balance determinations require careful evaluation. Such studies provide data on the amount of a nutrient that enters and leaves the body during the collection period. They provide no information on internal distribution or exchange. Directed towards establishing normal (minimal) requirements under standardized conditions, variables are limited [143]. Because the procedure is cumbersome and expensive, and housing in the protected environment of metabolic units is preferred, in order to obtain uncluttered data on the influence of single (usually dietary) variants on the utilization of the nutrient under study, the results are generally based on responses of few subjects under artificial stress-free conditions. Furthermore, young adults who volunteer to live regimented lives for long periods, isolated from normal outside activities, are likely to have relately placid temperaments. Metabolic studies done with volunteers living at home or in dormitories, but who are willing to consume only the monotonous diet provided in

metabolic units, and to collect all excreta, also are likely to comprise a selected group of individuals who do not reflect a wide range of dispositions. Even among such subjects, differences have been observed in the course of long-term metabolic studies, without altering dietary or environmental conditions [143].

Still another source of error is the pre-study nutritional status. Those with severe inadequacies (which might cause enzymatic dysfunction) might not adequately utilize high intakes until the metabolic abnormalities are corrected. Thereafter, positive balances should be maintained until the body deficits are repaired. On the basis of evaluation of 40 years of metabolic balance data from short-term and long-term studies, Hunscher [143] pointed out that subjects can maintain equilibrium even when their bodies are in actual debt, or below safe levels for any age or stage. She asked, "should we be complacent in accepting a lesser" than optimal "concentration in the body by being satisfied with equilibrium of flow resulting in unsaturation of tissues?"

Despite these defects, metabolic balance studies continue to provide important data — particularly when used in longitudinal evaluation of requirements during the course of an illness or physiological process [24].

Metabolic balance studies of magnesium requirements

Adults

Many of the metabolic studies, from which the 6—10 mg/kg/day magnesium intake recommendations for adults were derived [275], were done with free — living volunteers rather than in metabolic units. Such studies are subject to errors that result from failures to adhere to prescribed diets and from losses of samples. One may question whether the errors that result from selection of those with personalities suitable for the voluntary restrictions, and/or isolation from normal stresses, might not be at least as great. The meticulous balance studies, from which estimate of daily Mg needs of 300 mg or less have been derived, probably indicate minimal requirements [24, 143]. As with other nutrients, equilibrium can probably be established at sub-optimal and optimal intakes [143] as body deficits are repaired. The first clue that Mg supplements could produce strongly positive Mg balance, even after equilibrium had been maintained at much lower intakes, was provided by a long term study in a prison in 1926 [44] (Figure 4). One of two men who had been in strong negative Mg balance for the preceding two months, stored Mg during the weeks of supplementation (intakes of about 12 mg/kg/day). The other, who had a history of renal disease, merely lost less Mg. Perhaps he is the first recorded case of renal Mg wastage, about half the amount of Mg ingested daily, at low and high levels, was excreted in the urine. The study of healthy young college men fed a high Mg 8.9—11. mg/kg/day) liquid diet, such as was being investigated for patients needing tube-feeding, showed strong positive balances during almost all of the periods 44 week-long ([113], Fig. 5). One strong negative balance occurred during a stressful week of final examinations. A study of stable, ambulatory hospitalized men, who had been in Mg-balance on a diet that delivered about 185 to 300 mg of Mg/day, showed strongly positive balances early during Mg-supplementation that increased Mg-intakes 4-fold [275] The retention of Mg then gradually diminished until equilibrium was again established after several weeks of high Mg-intakes.

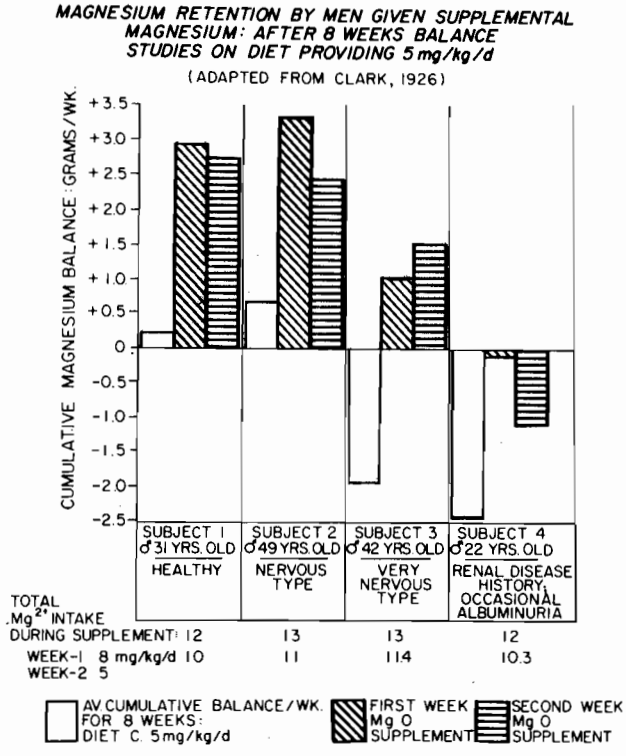

Fig. 4

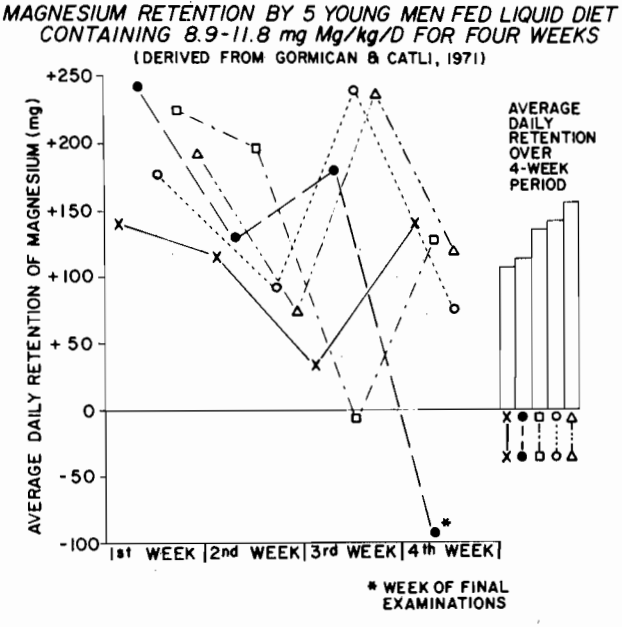

Fig. 5

Other long-term studies confirm the inadequacy of diets that provide under 5 mg/kg/day for men and suggest that even the RDA for women might not be sufficient for equilibrium. Two men with mean daily Mg-intakes (from selfselected diets) of 4.2 and 1.8 mg/kg/day lost 40±35 and 90±40 S. E. mg Mg/day [303]. Fifteen healthy young women, consuming a controlled diet that provided 265—305 mg Mg/day (or 4—5 mg/kg/day), were in mean strongly negative Mg balance over 3 consecutive 20-day-periods. (Figure 6) [148]. The diets provided high Ca/Mg and P/Mg ratios, such as are customary in American diets *(supra vide)*. They had strongly positive Ca-balances, which are not necessarily salutory, in view of soft tissue calcinosis that occurs in experimental Mg-deficiency [82, 102, 128, 203]. Their negative P-balances, despite their high P-intakes, are provocative, in view of the association of hypomagnesemia with hypo-phosphatemia (Review: [161]. The authors commented that the sustained Mg-losses on Mg-intakes considered adequate, suggest that higher daily Mg-intakes of 385 mg (or about 6 mg/kg/day) might be necessary to maintain a 140 lb (64 Kg) woman.

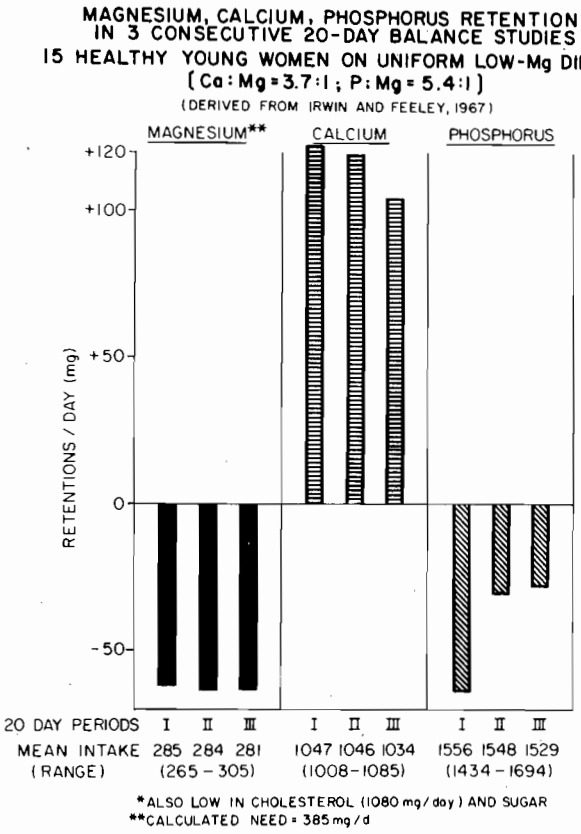

Fig. 6

Adolescents and children

Relatively few Mg-balance studies are available for those with rapid growth rates. Older adolescents (18 years) are commonly considered with teen-age boys as having high nutritional requirements. Girls that age are commonly considered with young adults. Mg-requirements of growing, developing infants, children and adolescents are greater than are those of adults — with the exception of pregnant or lactating women, and of those under stress or during convalescence.

Adlescent Girls (Figure 7): The first metabolic balance study of adolescent girls, in which Mg was measured, was a 1936 study [327] of 22 girls (11—15 years hold), eating self-selected diets that provided 6—10 mg/kg/d, or more than the RDA for Mg. Eight of the 22 girls, studied for 6 days, retained less than 10 mg of Mg/day — an amount that might be insufficient to meet the growth and development needs of this age group. On even lower Mg-intakes (190—195 mg/day, or 3.3—5.6 mg/kg/day), none retained more than 10 mg/day of Mg. The only girls not in negative balance were small, and thus received about 5 mg/kg/d [117]. In a subsequent study, in which Mg-supplements were given to raise the average daily intake to 286 mg, there were 9 balance periods with Mg-retentions of over 10 mg/day: 5 girls, when on a low zinc-intake, and 4 when on a high zinc-intake [118]. It is notworthy that the latter two studies showed that girls on marginal magnesium-intakes retained less Mg, when their zinc intakes were high. Low though the Mg-intakes were, during these studies, they were actually higher than that consumed by 15 14—16 year-old girls, whose 24-hour usual diets were analyzed [330]. The mean Mg-intake was 128 mg, with total intakes as low as 56 mg. Of 15 American girls, 17—18.8 years of age, fed a control-

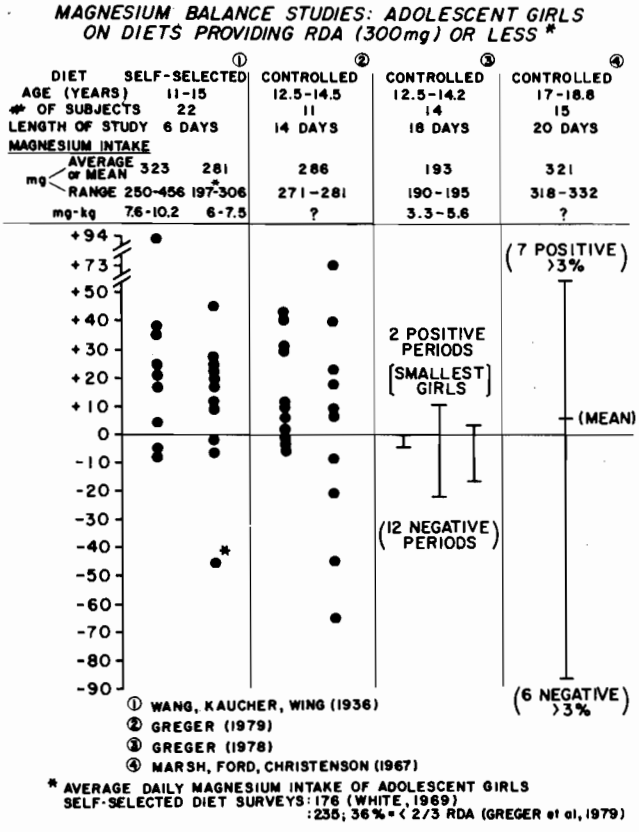

Fig. 7

led lacto-ovo-vegetarian diet that provided a mean Mg-intake of 321 mg/day, only 7 retained more than 3% [198]. The investigators commented that this indicates that girls up to 18 years of age have the higher requirements of adolescents, rather than the maintenance needs of adults. The higher than customary fiber content of the largely vegetarian diet, however, might have influenced the results, possibly decreasing Mg-absorption *(Infra vide)*.

Adolescent Boys (Figure 8): Magnesium requirements of adolescent boys have been correlated with their protein intakes, because of their rapid rates of growth and development [4, 263]. A study of boys who were 13—14 years old at the outset, and who gained 6 to 13 kgs from the beginning to the end of the study, which spanned two years, were in negative Mg balance when both protein and Mg-intakes were sub-optimal [263]. Increasing the protein intake to 93 gm, an amount in excess of requirements, improved the retention at the low intake of Mg. However, it was cautioned that the Mg retained with the high protein-intake, low Mg-intake, although probably adequate for maintenance of soft tissue content, was unlikely to meet Mg-requirements for growth and maturation. With the high Mg-intake of 740 mg, with low protein-intake, there were strongly positive Mg-balances the first year, but most had negative Mg-balances the second year. This might indicate the greater inadequacy of the 43 gm protein diet for the boys, the second year, when they were bigger. Strongly positive Mg-balances were maintained by most when both Mg and protein-intakes were high. The authors concluded that, since there is experimental (animal) evidence that a deficiency of Mg relativ to protein is harmful, whereas an excess of Mg relative to protein is probably not, Mg requirements should be set to permit an adequate retention ratio of Mg/N. They suggested that calculation of Mg requirements on the basis of Mg/N retention equal to or higher than the Mg/N ratio of the whole body, might yield a preferable figure for Mg needs during growth, than is provided by balance studies alone. Like the 17—18 year-old girls, whose balance studies indicated that their Mg-needs were that of younger adolescents, rather than the lower maintenance need of adults [198], with whom they are usually categorized, 18—20 year-old men went into negative balance on Mg-intakes of 3.5—7 mg/kg/day [4]. At those low to moderate Mg-intakes, changing the protein content of the diet from low (48 gm) to high (141 gm) exerted no influence on Mg-retention. When they were given 10.5 mg of Mg/kg/day, equilibrium to strongly positive Mg balances were achieved in half on the low protein diet, and in 5 of 6 when they were given a high protein diet.

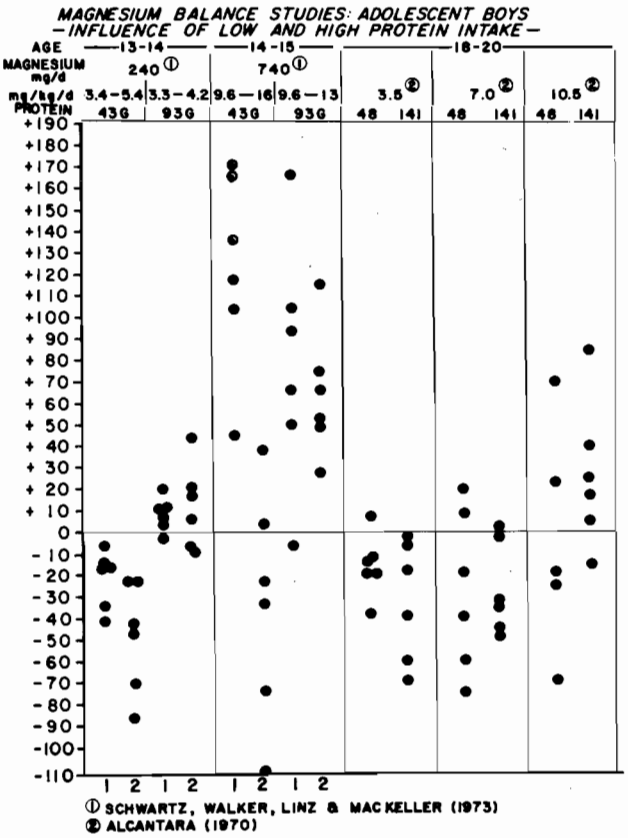

Fig. 8

Infants and children

The amount of Mg needed by infants and children is not certain. A review of the sparse metabolic balance data available in 1940 [67], correlated with tissue Mg-levels and growth curves, led to estimation of 10—20 mg/kg/day as the Mg-requirement. The optimal Mg-retention during growth and development has not been elucidated.

Infants: Infant Mg requirements depend upon the adequacy of maternal, and thus of fetal supplies whether the infants are premature, small for gestational age (SGA), born after complicated gestation or delivery, or whether they are full-term and healthy. For baseline data, we must ascertain how normal infants respond to normal milk diets, how supplements influence their Mg-retention, and how the mineral retention of breast-fed infants differs from that of those fed cows milk formulas or formulas adapted to resemble human milk. During the first week of life, normal, full-term infants, whose Mg-intakes provided 3.5—4.4 mg/kg/d from human milk, and 6.8 to 10 mg/kg/d from cow's milk formulas adapted to resemble human milk, retained small amounts of Mg [189, 287, 331 332]. Almost 5-fold more Mg was retained from cow's milk. However, infants at all ages retained far more Ca and P when fed cow's milk, as compared with those fed human milk, a phenomenon termed "supermineralization" of cow's milk-fed babies [299]. Despite the retention of large amounts of minerals by cow's milk-fed babies, they are much more subject to hypomagnesemic hypocalcemia, in association with hyperphosphatemia than are breast-fed babies [45, 271, 272, 206].

The much higher mineral content of cow's milk undoubtedly is the major factor in the high mineral retentions of formula-fed infants. The addition of vitamin D is also contributory. Metabolic balance studies have shown that vitamin D-supplements have little or no influence on Mg-retention of human milk-fed infants, but profoundly increase Ca- and P- retention of cow's milk-fed babies [285, 299, 331]. One of the studies [285] showed that infants given no vitamin D or up to 200 I. U. were in positive Mg balance during 44 metabolic study periods, and in negative balance during 8 periods. In contrast the Mg balances, of those who were given more than 200 units of vitamin D daily, were positive during only 16 of the test periods and were negative in 9. Breast-fed neonates showed slight rises in serum Mg in the first week, whereas vitamin D-free formula-fed infants showed a slight fall [111]. Adding 600 units of Vitamin D lowered the serum Mg further in bottle-fed babies, but not in infants on mothers milk. Administration of the vitamin D metabolite, 1-25-$(OH)_2$ D_3, raises the total and ionized Ca low-birth-weight infants during their first 48 hours, without affecting plasma Mg [42]. Such infants, who are likely to have low Mg-stores, are commonly treated with calcemic agents, which increase Mg-requirements [271], not necessarily reflected by low plasma Mg levels.

An early long-term study of infants fed formulas, without and with added fiber (celluflour) or spinach purée (which doubled thier Mg-intake) showed some interference, by fiber, with Mg-retention [262] (Figure 9). When the amount of Mg in the milk formula was doubled, by adding mineral salts equivalent to those in the spinach, all four of the infants retained more Mg. This study is noteworthy for two reasons: it shows that on Mg-intakes of 50—75 mg/day from cow's milk formula (the current RDA for young infants), the infants retained only enough Mg to remain in equilibrium- a scarcely desirable situation for rapidly growing babies. Furthermore, it shows that they did not retain the extra Mg provided by the spinach when they were under six months of age. This provides further justification for the recent observation that early infant-feeding of solid foods (as has been the practice for the past half century) is not desirable [168].

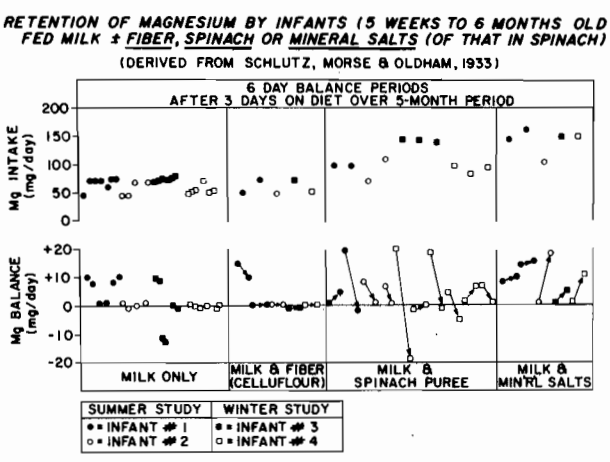

Fig. 9

Children: Early metabolic balance studies of Mg retention by 5 to 9 year-old children, consuming diets providing about the RDA of 8—10 mg/kg/day to as much as 25 mg/kg/day, showed that negative balances to retentions of no more than 10 mg/day were the general rule [56, 57]. One study showed that children on 10 mg/kg/day or less were in negative balance; most of those receiving over 18, to as much as 40 mg/day of Mg, retained very large amounts of Mg (120 to 440 mg/day) during their 4 to 5 day balance studies [231]. Whether such retentions can be verified, and how long they would persist, would provide important information as to optimal Mg-nutriture of children. Subsequent studies have shown that young children given diets low in Mg (4—9 mg/kg/d) maintain Mg-equilibrium or retain about 20 mg/day [125]. A study in which the same children were given diets providing different levels of Mg, showed strong Mg-retentions on the high (13—18 mg/kg/day) versus the low (< 10 mg/kg/day) intakes.

Anabolic processes requiring more magnesium

Those forming new tissues, whether as a result of growth and development, athletic training, convalescence, or pregnancy and lactation, have increased nutritional needs. The supply of magnesium, which plays important roles in nucleic acid and protein synthesis and in numerous enzyme-functions [128, 253, 310, 318, 321, 322], often insufficient to maintain equilibrium during stable phases, can fall to critical levels during growth, development, and repair processes. Further study is needed to define how much Mg is necessary for *optimal* function at those times.

Pregnancy and lactation

The condition, during adult life, in which Mg-requirements have recently recognized as being elevated (RDA = 450 mg/day) are pregnancy and lactation [101]. Nevertheless, pregnant women whose Mg-metabolism has been studied, selected diets that provide less than half that amount [14, 144]. Negative Mg-balances have been found in middle-class pregnant American women [14]. Review of the literature shows that the Mg-intake during pregnancy has been declining since the turn of the century [271]. The first report found was of a 1914 study in Germany [164] showing that on daily Mg-intakes of 338—510 mg, pregnant women retained from 97—159 mg/day in the last trimester. Longterm studies of pregnant women in Finland [136] and in the United States [149, 141] showed that in Finland, where the Mg-intake during pregnancy was 177—389 mg/day, there were many negative balance periods (Figure 10). A healthy

American quadripara, whose Mg-intake during the last half of pregnancy was high (590—615 mg/day), remained in strongly positive Mg-balance during her last trimester [141]. An American teen-aged primipara with a poor nutritional history and whose Mg-intake was below the RDA, retained less Mg during the last two lunar months of her pregnancy [140]. It is worth noting, here, that adolescent mothers, whose own Mg-needs are likely not to be met, are particularly at risk of gestational Mg-deficiency.

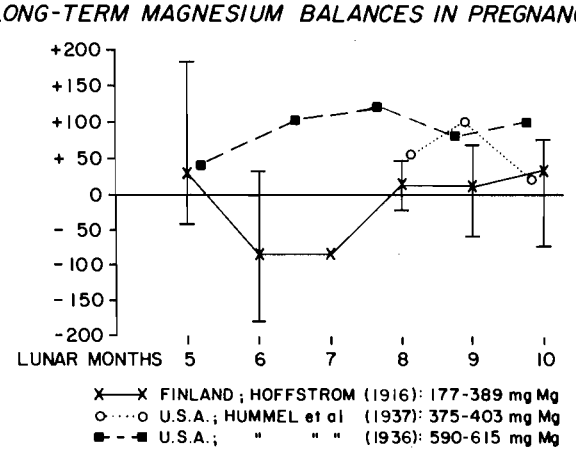

Fig. 10

The optimal Mg-intake during gestation remains to be determined, but there are several findings that suggest that gestational Mg-inadequacy might be more common than realized. Pregnant women tend to develop somewhat lower serum Mg-levels than are seen in age-matched non-pregnant women [61, 121, 221]. Correction for hemodilution has shown the hypomagnesemia to be real during the first half of pregnancy and in the last month [61]. Hypomagnesemia has long been recognized in eclampsia [1, 121, 126]. Mg-therapy has been used to control pre-eclampsia and eclampsia since the first quarter of this century [167]. On occasion, investigators have wondered whether the similarity of some of the toxemic manifestations to those of Mg-deficiency might indicate that the improvement on Mg-therapy might reflect repletion of a deficit [75, 98, 121, 263, 271, 274]. It is also possible that Mg-inadequacy might also contribute to gestational hyperparathyroidism, which is so common as to be termed "physiologic" [54]. The occurrence of hypomagnesemia, hypocalcemia, and hyperparathyroidism, especially in the third trimester [28, 54, 61, 121, 221, 329], suggests that hyperparathyroidism might result from the mineral inadequacies, rather than be physiologic [267, 271]. In fact, the development of infantile hypocalcemia is considered an indication of need to test the mother for hyperparathyroidism [18, 105, 124]. Maternal hyperparathyroidism has been detected in mothers of infants with neonatal hypomagnesemic hypocalcemia [60, 85, 213].

The vulnerability, during the third trimester, to gestational abnormalities to which magnesium indequacy might be contributory, might reflect the fetal needs for Mg during that time [48, 271, 333, 334]. It has been estimated that the daily Mg content of the fetus doubles during the ninth and tenth lunar months [48, 333]. Perphaps the improved perinatal salvage rate (10% versus 25—35% fetal loss) of infants of eclamptic women treated with Mg, as compared with those otherwise treated [234, 343, 345] might reflect meeting of fetal needs.

Recovery after starvation

Sudden cardiac deaths have been reported during total starvation [52, 107, 291], during refeeding after total starvation [107], and while dieting on a liquid protein preparation [207]. The latter patient had a low serum magnesium level (1.5 mgEq/L) that did not rise to more than 1.67 mEq/L despite an infusion with Mg, and she died of ventricular fibrillation and cardiomyopathy. Because short — and long-term fasting of non-obese volunteers [47, 298] and obese patients [64, 65] results in substantial Mg-losses that are not always associated with low serum Mg levels, attention should be paid to meeting Mg-needs both during fasting and re-feeding.

It has been shown that malnourishment, with resultant metabolic abnormalities, interferes with adequate utilization of nutrients which is reflected by delays before positive balance (e. g., of Ca) is achieved with repletion [243]. Evidence that this holds true for Mg was provided by the study of Mg-balances of starved patients, early after admission to the hospital and during Mg-repletion [205, 206] (Figure 11). Strongly negative Mg balances persisted on diets providing 800 mg

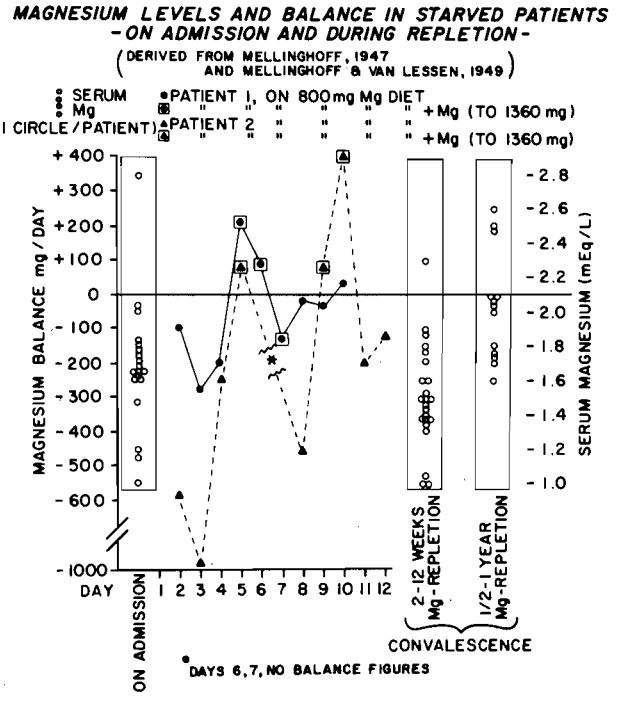

Fig. 11

Mg/day. Supplements (Mg lactate), that increased the daily Mg-intake to 1—1.36 g/day produced retention, but losses recurred when the Mg-rich diet, alone, was fed. The investigators reported that subnormal Mg-retention was only gradually corrected during the half to one year period of observation. Possibly such patients are in need of very high Mg-intakes. Noteworthy are the essentially normal serum Mg levels is 21 starved patients, which fell to sub-normal levels during the first 12 weeks of re-feeding and Mg-repletion, and rose to normal in most only after a half-year of convalescence.

The Mg-deficit of starvation is contributed to by the associated increased production of lactic acid and lactate, and by ketone acidosis — conditions that increase urinary Mg-loss [19, 153, 180, 181]. In such instances, Mg-deficiency can be masked by the egress of tissue Mg, whether the metabolic abnormality is caused by decompensated diabetes mellitus [201, 202, 218], starvation [64, 65, 298], or the malnutrition of chronic alcolholism [156]. The stress of starvation or of alcohol-withdrawal is another factor in Mg-depletion. The stress hormones cause Mg-loss directly and as a result of lipolysis, with release of free fatty acids [239, 241] (Figure 3). During the acute phase of alcohol-withdrawal, free fatty acids increase in the plasma [204], with resultant decrease of serum Mg [93, 95, 96]. Starved obese patients have ample fat stores to yield free fatty acids; those taking liquid protein diets to lose weight have an added risk factor: the increased urinary Mg-excretion produced by protein loads [68, 180].

When patients are malnourished as a result of starvation or disease, and are refed without consideration of the high Mg-needs to make up for tissue-losses and meet the requirements for new tissue-formation, there can be serious consequences [339]. Children with protein-calorie malnutrition, for example, deteriorated rapidly and developed cardiac complications when Mg was not provided during the high caloric-protein treatment [33, 34]. Similarly, the malnutrition and vitamin (B_1) deficiency of alcoholics can be refractory to therapy until the Mg losses are repaired [339].

Magnesium requirements of the aged

Metabolic balance data are lacking for aged people, but there are fragmentary findings that suggest that their Mg-requirements are likely not to be met by their diets. A survey in Belfast shows that the diets of institutionalized and non-institutionalized old men and women provided from 160 to 230 mg/day [312]. The decreased intestinal Mg-absorption by old, as compared with young normal subjects and patients [154, 216] puts them into further Mg-deficit. Serum Mg levels of aged subjects have been reported to be lower than in young adults [131, 245] and to be about the same [159, 304]. Since the Mg-retention of aged mice is much less than that of young mice [63], and the life expectancy of rats kept on low Mg-intakes for their entire lives is reduced [133] definition of Mg needs of aging people, and the effects of Mg-supplementation seems worth exploring.

Dietary factors that increase magnesium requirements

Many nutrients increase Mg-requirements when supplied in excess (Reviews: [71, 72, 76, 166, 180, 269]). These include calcium and calcemic agents like vitamin D, phosphate, phytate, sodium potassium, protein, carbohydrate and fat. Emphasis on the role of saturated and unsaturated fat on cardiovascular disease [8, 9] has led to recommendations for major dietary changes that have been questioned [100, 184, 296]. Generally disregarded is the effect on Mg-utilization of the dietary fat. The newer nutritional approach to hyperlipidemia and atherosclerosis — that of increasing the fiber content of the diet [171, 217, 308] is one that interferes with Mg-absorption *(infra vide).* Since the availability of Mg has clearly been shown to affect the degree of cardiovascular damage in many experimental models (Review: [244, 271, 273, 278, 279, 300, 301]) its availability in diets that alter fat and fiber intakes might well be critical in influencing the prophylactic efficacey of such diets.

Effects of dietary eat on magnesium requirements

As early as 1918, it was shown that fat interfered with Mg-absorption [216]. Mg was better absorbed from meals that provided 436 mg/day than it was from meals that provided 314 mg Mg/day and that were rich in butter fat. The two children (5 and 8 years of age) were in strongly negative Mg balance having 3-days of high-fat diet. In another early, short-term balance study [29], substitution of butter for margarine, in a diet rich in Mg (800—832 mg/day), resulted in slightly increased Mg-retention by each of 4 young women. In two, negative balances were converted to positive. Linoleic acid has also decreased Mg-utilization by young men [125, 149] and women [148] fed diets much lower in Mg. Mg-retention fell as the linoleic acid content was increased. At Mg- intakes of 4—6.3 mg/kg/day, or 300—370 mg/day, most of the young men were either in Mg-equilibrium or slightly negative balance on controlled diets providing 9—10% of the free fatty acid; Mg-losses increased as the linoleic acid content was increased to 30% of the calories. Young women, who lost an average of 63 mg Mg/day while on a controlled diet that provided 4.2—5.4 mg Mg/kg/day (*supra vide,* Figure 6), showed rising blood lipids, even though the dietary fat was low (1 g/day) (Figure 12). This observation is analagous, though lesser in degree, to the experiments that showed that Mg-deficiency intensified the hyperlipemia of animals fed hyperlipemic, atherogenic, thrombogenic, or glucose-rich diets [129, 142, 249, 259, 260, 280, 313—315]. Of particular interest is

the increase in levels of β- and pre-β lipoproteins in Mg deficient rats, and in pigs [224], that fell with Mg-supplementation, since preliminary clinical studies suggest a similar effect of Mg-supplements in patients with hyperlipemia [127, 178, 226, 293]. Since increasing the Mg-content of cardiovasopathic diets has protected animals against tissue lesions [224, 259, 260, 271, 279, 289, 300, 301] members of high-risk families and populations, who might have high Mg-requirements, might benefit from Mg-supplementation. Diets designed to meet official recommendations to lower the total intake of fat to 35% or less of total calories in order to reduce the risk of cardiovascular disease, provide less than the RDA for Mg [200]. Possibly the prophylactic effect of such diets might be improved by correcting sub-optimal Mg-intakes. The optimal Mg-intake of those with abnormal handling of fat and who are vulnerable to cardiac and arterial disease requires study.

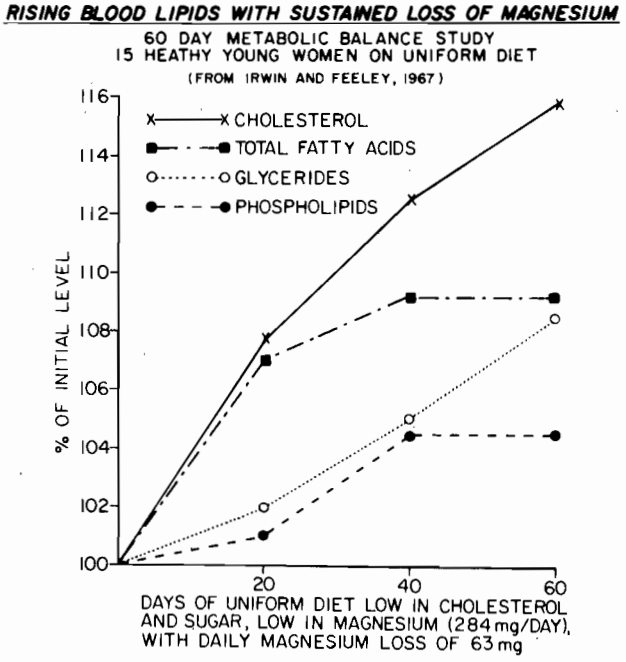

Fig. 12

Effect of fiber and phytates on magnesium requirements

The incidence of many chronic diseases is lower among population groups consuming diets rich in fiber than among those eating refined foods low in fiber. This observation led to the official recommendation [308] that Americans increase their intakes of fiber. Careful scrutiny of findings from early metabolic balance studies discloses much valuable information that complements the newer work which shows that fiber causes losses of minerals, including Mg. The effect of phytate on Ca, P, Mg and trace minerals has attracted interest. The first long-term metabolic study, that compared the influence of bread made of white or brown flour, with and without phytate or Mg (added to the white flour) showed that phytate interfered with the absorption of the 2-fold greater amount of Mg in the brown bread [186, 187]. When the same amount of Mg (as carbonate) was added to white bread, its retention was improved. A subsequent study [323], in which balances were determined in two men, studied for 14—15 consecutive weeks, on diets with low- and high-fiber breads. They showed initial profound Mg-losses when a pound of high-fiber bread was substituted for other food (Figure 13). The retention of Mg improved over the 7 and 8 weeks on that diet. They were in Mg-equilibrium when white bread was substituted, despite the smaller amount of Mg eaten. All of the 12 Ceylon medical students on a controlled diet resembling what they usually ate: largely brown and white rice, vegetables, and moderate amounts of animal protein [53] were in Mg-balance (Figure 14). When white rice was replaced by brown rice, they all retained less Mg, five going into negative balance over the the 5-week study. Providing only white rice resulted in stronger positive Mg-balances, especially during the weeks of consumption of a variety of rice that was rich in Mg. Women consuming uniform diets low in Mg and fiber, or with an adequate Mg intake provided by oatmeal, showed differences depending on their weight [125]. The small women tended to remain in equilibrium, or lost less Mg on the low-Mg diet or on the phytate-rich diets, than did the larger women. The marked change in balance in the same period is notable, particularly among the women whose Mg-intakes were below 4 mg/kg/day on the low-fiber diet, and whose intakes were not high on the high-fiber diet.

Mineral balance studies, undertaken more recently because of zinc deficiency in the Middle East, that is related to high fiber-interference with its absorption [232], have shown that whole grain breads also interfere with Mg-absorption [40, 243]. During 2 20-day metabolic balance periods, 2 young Iranian men were

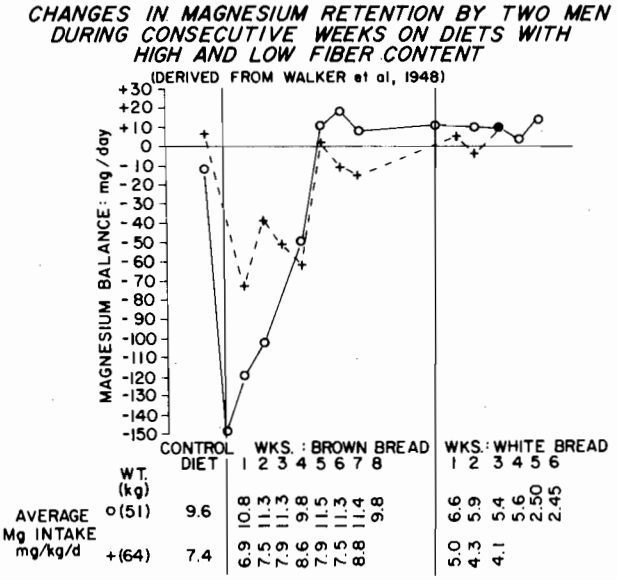

Fig. 13

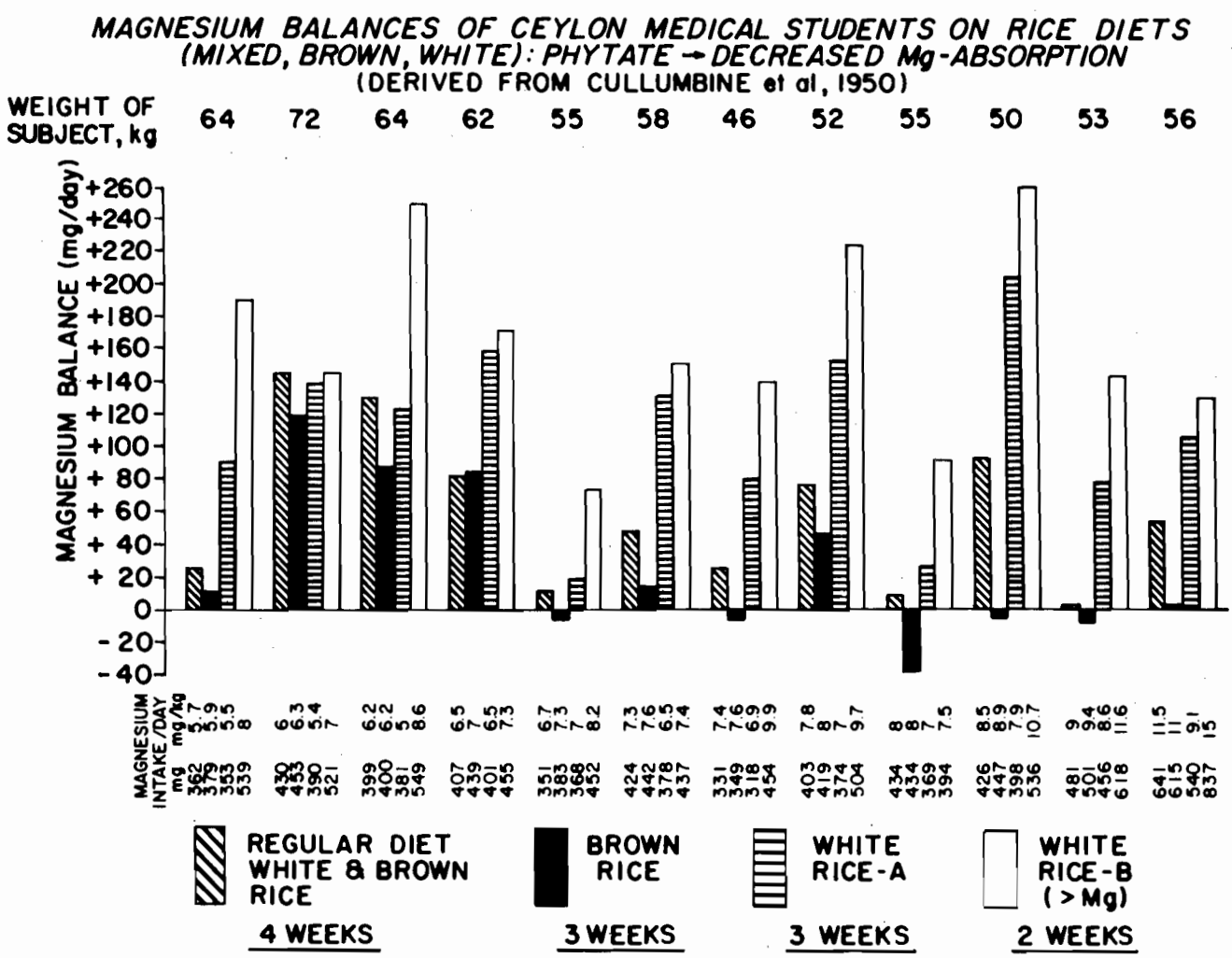

Fig. 14

in Mg equilibrium or slightly negative balance when half of their food energy was derived from flat bread made from refined flour [243]. When their bread was made with unrefined flour, each went into negative Mg balance (44 and 129 respectively) despite the two-fold greater Mg content of the whole grain bread. A comparable longer-term study of 2 young Americans showed that initially strongly negative Mg balances became positive or less strongly negative when flat bread made from refined flour was substituted for whole grain flat bread [40]. No adaptation to the high fiber diet was observed in the study in which consecutive balance results were reported [243].

Fiber added to controlled diets has also interfered with Mg-retention. Studies of adolescent and pre-adolescent boys who were given diets containing 420 or 336—333 mg Mg/day, showed that both hemicellulose and cellulose increased the negative Mg balance that was observed during most control periods [66, 194]. Similarly, men [160] and young women [228] retained less Mg when fiber was added to their diets or when they consumed natural fiber-rich diets. There was not a consistent trend toward decreasing losses in six consecutive 5-day periods in the natural fiber-rich diet. Noteworthy, is the lack of correlation of plasma Mg levels with retention of Mg [288] (Figure 15). Most of the studies with diets of added fiber gave less protein than is consumed by most Americans. A more modest intake of fiber, added to a diet richer in protein, has exerted little effect on magnesium retention by men living in a metabolic unit and consuming uniform diets providing about 300 mg/day [258].

Other nutrients that increase magnesium requirements

Since Mg is important in carbohydrate metabolism and in protein and nucleic acid synthesis, those consunming diets rich in proteins and sugars have high Mg-needs. Contributory to the risk of Mg-inadequacy of such privileged people is the increased urinary excretion of Mg that follows protein and glucose or lactose-loads *(infra-vide)*. Those whose high protein-calorie diets are supplemented with large doses of vitamins and minerals are at further risk of Mg-deficiency.

Protein: The physiological state and activity, and the prior nutritional status, influence the effect of protein-intake on Mg-needs. During protein-synthesis and formation of new tissue by growing and developing

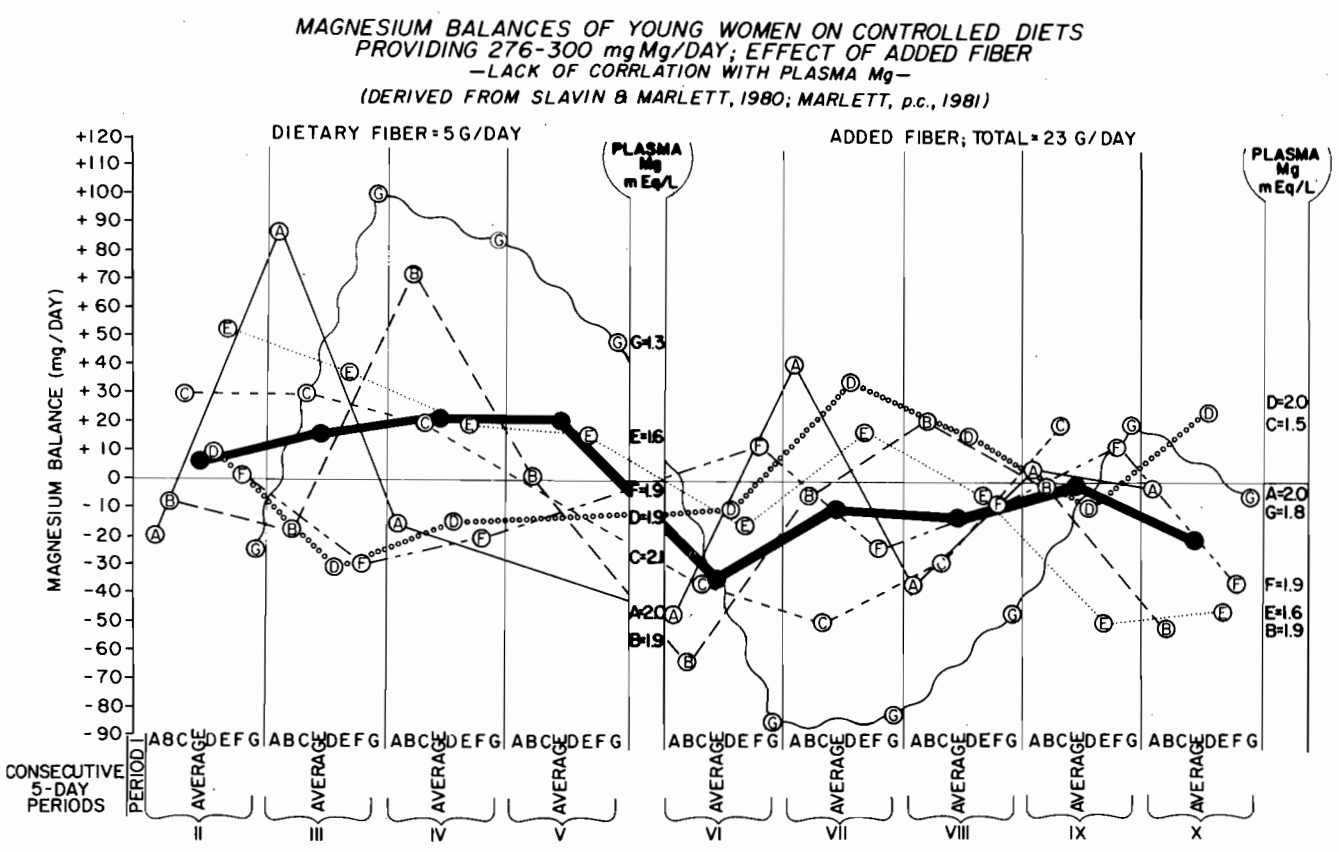

Fig. 15

children, by athletes-in-training, by pregnant or lactating women, and by those recovering from starvation or wasting illness, high-protein diets increase Mg-needs.

Young adults, consuming controlled diets that provided 438 to 605 mg Mg (6.5 to 8.6 mg/kg/d) and moderate (45—70 g) or high (100—130 g) of protein, absorbed and retained less Mg on low-protein than on high-protein diets [188]. Of the 3 young men, whose Mg-intakes were 7—8 mg/kg/d, 2 were in negative balance (when sweat loss was considered) on the low, but not on the high-protein diet. The young woman in that study, whose Mg-intake was 5.8—6.5 kg/kg/day, was in positive balance on both protein diets. In another study [294] of the effect of protein on Mg absorption of young women, whose controlled diets provided more Mg (5—7 mg/kg) than the RDA, all 10 were in strongly positive Mg balances on low protein intakes (47 g protein). Providing 30 g of animal protein to a basal controlled low-protein diet, fed to young men (which increased their Mg-intake from 303 to 362 mg/day), or adding 100 mg of Mg as $MgCO_3$ to the basal diet, converted the negative Mg balance in 5 of 6 men to positive [195]. Young women on low Mg intakes (2.5—4 mg/kg/day) were in strongly negative Mg-balance on the very low protein-intake of 20 g, in Mg-equilibrium when the dietary protein was increased to 30—34 g, and in positive balance (+24) on a protein intake of 48 g [145]. Young adolescent boys retained more Mg from a low Mg-diet (240 mg or 3.4—5.4 mg/kg/day) when the protein intake was increased from 43—93 g (263, Figure 2). When the Mg-intake was adequate for growth and development (740 mg, or 9.6—16 mg/kg/day), the protein intake exerted less effect on the Mg balance. Older teen-agers (18—20 years of age) tended to remain in negative Mg balance on low and high protein intakes, when their Mg-intakes were below 10 mg/kg/day, but most went into positive Mg-balance on diets rich in both Mg and protein (4, Figure 8).

In brief, the studies indicate that when intakes of both protein and Mg are low the Mg balances tend to be negative. Increasing dietary proteins to levels of "low protein" diets, from extremely low levels, improved the Mg-retention of young women, whose Mg-intake was kept low [145]. However, 18—20 year-old on low Mg-intakes lost more Mg when their dietary protein was increased from low to high [4]. Young adolescent boys receiving sub-optimal amounts of Mg retained more Mg when their protein-intake was increased from low to normal [263]. At marginal Mg intakes (equal to the RDA), young men also retained Mg better on normal than on low protein diets [195]. On high Mg-intakes most of the balance periods of men and women [188], and of young and older adolescent boys [4, 263] were positive, whether the protein intakes were low or high. Additional to the improved utilization by boys on the high Mg, low or high protein-diets, as compared with that on the low Mg-diet

[263], the retention of Ca was improved [264]. Nitrogen balance was about the same on the low-protein diet, on the high and low Mg-intakes, and somewhat better on the high-protein diet when the Mg-intake was also high [263]. The protein intake generally being high, and the Mg-intake low in countries with diets resembling that in America, it would seem advisable to increase the Mg-content of the diet, or to give supplements so as to provide 6—10 mg/kg/day to adults and twice as much to those with active anabolic processes or under stress.

On the other hand, protein-loading has acutely increased urinary Mg excretion [68, 180, 181]. Administration of 50 g of gelatin (additional to the subjects' customary diet) resulted in moderately increased urinary Mg-output of 12 to 24 mg/day over the 6-day study [68]. Ingestion of 50 g of casein by 4 men increased their mean renal excretion rates of Mg from 3.3 to 5.3 Eq/minute [181]. This effect of protein loads might have been contributory to the hypomagnesemia of a patient who developed fatal arrhythmia during refeeding after a liquid protein diet for obesity [210]. The recovery syndrome of children with protein-calorie-malnutrition, during protein-calorie refeeding, includes cardiac and nervous system disturbances, that can be prevented or treated by addition of Mg to the diet [33, 34]. In view of the direct and indirect evidence that high protein intakes increase Mg-needs, its status should be evaluated in those synthesizing protein and building new tissues, particularly those at risk of prior Mg-inadequacy or loss. When such evaluation is not feasible, providing such patients with at least as much Mg as is required by young adolescent boys (>10 to 16 mg/kg/day [263] would seem to be the prudent course.

Effects of sugar, alcohol, and salt on magnesium requirements: Diets in America and in other industrialized countries are generally high in sugar and salt; moderate to heavy alcohol-consumption is common. Thus, the studies showing that each causes Mg-loss is germane to calculations of Mg-needs.

Glucose: An oral glucose dose of 100 g caused almost as much urinary Mg-excretion by healthy young men, as did an ample breakfast of cereal, milk, egg, ham, bread, butter, jam and tea, or as did an amount of Mg and Ca equal to that in the meal [135]. Glucose interferes with renal tubular reabsorption of Mg [173—176, 180]. Lactose and galactose also increase magnesiuresis [19, 180]. Oral glucose-tolerance tests of normal children and adolescents (1.75 g glucose/kg to a maximum of 75 g) caused a mean 9% decline of serum Mg on the first half hour, that remained 5% below control values by the 4th hour [249]. This effect was attributed to glucose-enhancement of cellular uptake of Mg in normal children, that was not as efficient in those with pre-clinical or clinical diabetes.

These clinical studies of the influence of acute glucose loads on Mg-excretion in urine, and the laboratory animal evidence that glucose (and insulin) increase tissue Mg-uptake [2], support the observation that diets rich in sugar increase Mg-needs [72, 76, 166].

Alcohol: The severe Mg-depletion caused by chronic alcoholism is well recognized, although not always treated [92, 94, 97, 156]. Even moderate amounts, taken before and with meals, increase urinary Mg-loss [157, 190, 193], thereby increasing Mg-needs.

Sodium: Glucose loads augment the renal tubular reabsorption of Na, at the same time as they decrease Mg-reabsorption [175, 176]. Greater Na-loads such as are provided when saline is used to expand the extracellular volume, decrease serum Mg levels and increase urinary Mg excretion [26, 134, 211, 325]. Fasting obese patients, whose Mg losses exceeded the amount calculated to have been derived from catabolized lean tissues, had only slightly lower than control serum Mg levels, unless they received Na Cl supplements [64]. Those given 45 mEqNa daily exhibited as much as 25% drops in serum Mg by the 20th—30th day of fasting. The reciprocal of this finding is the Na and water retention seen in Mg-deficiency, and the loss of Na (and water) produced by Mg-repletion [36, 120, 230].

Calcium and Vitamin D: Ca-excess, such as has intensified lesions of Mg-deficiency in experimental animals (Review: [271]) is not characteristic of the human diet. In the United States and Finland, where consumption of milk and cheese is high, where (in the U. S.) milk is fortified with therapeutic amounts of vitamin D, and taking vitamin-supplements is common, the calcemic effect of vitamin D, which favors Ca intestinal absorption and renal tubula reabsorption over that of Mg [325], might make critical the Mg-inadequacy of the usual American and Finnish diet [158, 268, 271, 311]. The hyperlipidemia caused by even moderate vitamin D excess, or by hyperreactivity to vitamin D [86, 182, 183, 271] might further increase Mg-requirements.

Phosphates: Excess PO_4-intake is common in the industrialized world, particularly among those consuming large quantities of colas [185]. It is not uncommon for the PO_4 — intake to exceed the RDA 2 to 3-fold (Figure 1). Such high intakes of PO_4, particularly among those eating highly salted foods and whose Mg-intakes are marginal or low-might well increase the risk of heart and bone damage (Review: [271]). Are such dietary imbalances the human analogue of the experimental cardiac necrosis produced by Na_2HPO_4, which is protected against by Mg and KCl (Reviews: [16, 171, 273, 279, 283])? When high vitamin D, fat, protein and sugar content of the diet is added, a cardiovasopathic diet that causes spontaneous myocardial infarction in several animal species [244, 289, 300, 301], and against which increasing the Mg content of the diet 5-fold has been protective [247]. High dietary PO_4 interferes with Mg-absorption (Reviews: [128, 166]) and increases the amount of Mg needed for normal function and survival by experimental animals [32, 102, 214, 215, 225]. Thus the amount of

Mg required by those consuming diets rich in PO_4 deserves investigation.

Other vitamins, zinc, and magnesium needs

Abnormalities in metabolism of vitamins B_6 and B_1, whether caused by genetic disorders or by diseases that cause malabsorption, or whether caused by malnutrition, can result in abnormalities of enzyme systems that are dependent, also, on Mg. Vitamin E and zinc are additional nutrients with interrelationships with Mg that might influence Mg-requirements.

In these days of use of high doses of vitamins and trace minerals, it is important to determine the effect of such "megadosage" of trace nutrients on the macromineral-Mg- that is usually consumed in suboptimal amounts. Overuse of water-soluble vitamins is generally less of a problem than is overdosage with fat-soluble vitamins, which are stored instead of being excreted in the urine. However, excesses of even readily eliminated nutrients can create difficulties if imbalances result.

Vitamin B_6: Interrelationships of Mg and B_6 deficiencies have been recognized since it was found that the acute Mg-deficiency syndrome was more rapidly produced in rats that were also deficient in vitamins B_6 (and B_2) than in those deficient only in Mg [114, 115]. The similarity in the two deficiency disorders was also noted early [172]. Experimental B_6 deficiency has caused loss of tissue Mg [3]. It has been associated with temporary hypermagnesemia and then hypomagnesemia as the tissue Mg is depleted [15, 70, 248]. Several of the enzymes that require pyridoxal phosphate as a coenzyme, such as pyridoxal phosphokinase, kynureninase, transaminases, amino acid decarboxylases, transaminases, and cystathionase, as well as Schiff base formation with amino acids, also require Mg [15, 172, 191, 310, 318].

It is, thus, not surprising that Mg deficiency and B_6 deficiency produce comparable clinical disorders, or that treatment with either Mg or B_6, or both, have been found effective in several clinical conditions in which one or the other of the nutrients has been investigated. For example, infantile convulsions have been caused by an infant formula deficient in B_6 [25], and by hypomagnesemia (Review: [271]). There is evidence that a genetic vitamin B_6-dependent disorder that is characterized by convulsions, is caused by interference with the glutamic acid gamma-aminobutyric acid (GABA) system [266, 305]. The enzymes involved are amino acid decarboxylases and transaminases, that require both B_6 and Mg for activation. B_6 therapy is specific; the effect of Mg has not been studied in this disorder. Three additional B_6-dependent diseases with central nervous system damage (mental retardation) are cystathionuria, homocystinuria and xanthurenic aciduria [106]. The B_6 enzymes involved are cystathionase and kynureninase, both of which also require Mg [172]. Since the response of these diseases to B_6 — supplementation is incomplete [106], it may be that Mg-requirements are also high. B_6-dependent anemia [106] might also be Mg-dependent. The role of Mg deficiency in erythrocyte survival having been clearly demonstrated [46, 81, 82, 84].

Whether pyridoxine and/or Mg-deficiency during pregnancy can contribute to infantile B_6-dependent diseases has not been determined. However, B_6-depletion during pregnancy has been reported for many years [31, 316, 317]. Although Mg is a favored treatment for eclampsia, the proposed role of Mg deficiency in the pathogenesis of gestational and fetal abnormalities [267, 271, 274] has not gained as wide acceptance. The B_6-dependent disorders having a high familial incidence, it should be possible to test the hypothesis that meeting unusally high requirements of both nutrients might correct the chemical abnormalities, and might be more effective in the clinically manifest disorders than correcting only one of the deficiencies.

The clinical efficacy of a combination of pyridoxine and Mg [109, 233], and of Mg alone [154, 163, 207, 208], has been seen in patients with calcium oxalate urolithiasis. It seems plausible that the metabolic abnormality that results in such urinary tract stones in geographic areas with low Mg-content of drinking water [163], might be one in which there are higher than RDA Mg-needs. The enhancement of clinical improvement by the use of both B_6 and Mg [109, 233] supports the premise of conjoint activity. However, there is experimental evidence that high B_6-intake can intensivy Mg-deficiency [162].

This finding points to the need for further study, and to the possibility that megavitamin therapy might increase Mg-requirements.

Vitamin B_1: Mg-deficiency interferes with response to thiamine in B_1-deficient rats [150—152, 338, 340] and in alcoholic patients a not surprising finding in view of the Mg-dependece of enzymes requiring B_1 (Review: [310]. A genetic metabolic disorder of B_1 metabolism, subacute necratic encephalopathy (SNE) is similar to *Wernicke*'s encephalopathy, and might respond better to Mg plus B_1 than to B_1 alone. An infant with this disorder has responded somewhat better to B_1 when Mg was added to the regimen (*J. Cooper*, personal communication). Another infant has been found to have impaired B_6 metabolism [78], a further clue to a possible interrelationship with an abnormality in Mg metabolism.

Administration of thiamine to B_1 + Mg deficient animals has intensified Mg-deficiency [150, 339, 340] and has increased the blood levels of serotonum [151, 152]. Long-term high dosage B_1 therapy is common in chronic alcoholics, who have Mg-deficiency and high Mg-needs, and in those self-medicating themselves with megavitamins, whose Mg-needs might thereby be increased.

Vitamin B_2: There are only few data on Mg/B_2 interrelationships. Diets deficient in B_2, B_6 and Mg or in B_2 and Mg caused more signs of Mg deficiency on

higher Mg-intakes than when only the Mg was deficient [114, 115]. On the other hand, a high intake of riboflavin increased the susceptibility to electrical stimulation of Mg-deficient rats [212], thus high dosage B_2 supplementation, whether during recovery from alcoholism or by vitamin — faddists, might increase the risk of Mg-deficiency.

Vitamin E: Experimental vitamin E deficiency has lowered tissue levels of Mg in calves [27], rats [90], and rabbits [342], and has precipitated lesions of Mg deficiency in rats [112]. Administration of Mg has prevented signs of E-deficiency in rats [265]. No data have been found on the influence of high dosage vitamin E on Mg-requirements in man.

Zinc, Vitamin B_6 and Mg: Both Zn and Mg are required for pyridoxal kinase [191]. Pyridoxine is necessary for tissue Mg-uptake [3], and might also be for that of Zn, though there are different laboratory findings [108, 139]. High oral doeses [295], but not intravenous doses [180] have decreased Mg-retention. Metabolic balance studies of adolescent girls showed less Mg-retention from marginal Mg-diets, when the dietary Zn was high than when it was low [117—119]. High Zn-intake did not adversley affect Mg-balance when Mg-supplements raised the daily intake to over 10 mg/kg. More attention is now being paid to Zn deficiency, even in developed countries [23, 122], and Zn-supplementation, prescribed and taken without medical supervision. The influence, on Mg-needs, of high Zn-intake, should thus be ascertained.

Discussion and conclusions

There is a substantial gap between the typical Mg-intakes of young Americans and even the RDA, which is based on studies designed to determine minimum requirements. When the many factors that increase Mg-requirements are considered, one can conclude that absolute or conditioned Mg-inadequacy is common in the industrialized world. Epidemiologic evidence that soft water, and diets with high Ca/Mg ratios increase vulnerability to cardiovascular disease [10, 11, 51, 99, 197, 219, 220] indicates that when the Mg-intake is low, that provided in drinking water can be critical. Nonetheless, determination of the Mg-status is not routine even in hospitalized patients whose diseases and treatment cause Mg-loss. The possiblity that long-standing sub-optimal Mg-intakes might be contributory to disease is disregarded by the majority of physicians, epidemiologists, and nutritionists.

It is largely from the early metabolic balance studies that have come the data indicating that adults might require 6—10 mg/kg/day of Mg, and that infants, children, adolescents, and pregnant women probably need considerably more. Most of the realtively recent studies have focussed on the least Mg at which equilibrium can be maintained. The conclusion reached, after evaluation of metabolic balance studies during the first half of this century, that metabolic balance can be maintained even in the presence of deficiency, and that a new equilibrium is established at intakes more likely to meet needs [143], has not usually been applied to Mg studies.

One should keep in mind the normal body's ability to limit Mg-loss and to adapt to marginal intakes for prolonged periods. For example, rats have shown the capacity to adapt to Mg-intakes low enough to cause signs of deficiency early, that later disappear on the same (Mg-deficient) diet, with return of normal plasma Mg levels [133]. Despite this seeming tolerance of low dietary Mg, the animals'ability to withstand stress, and their life spans were reduced as compared with controls on normal diets. This important study demonstrates the invalidity of Mg-restriction studies as determinants of Mg-requirements. Interpreting obligatory urinary Mg-losses by healthy subjects on diets extremly low in Mg as the amount required [20], or calculating the minimal amount of dietary Mg that will prevent hypomagnesemia [199], yield grossly inadequate estimates of Mg-requirements. Metabolic balance studies at low or marginal Mg-intakes, that show little or no net loss, might reflect the normal subjects' capacity to adapt to periods of sub-optimal Mg-intakes, or (in the case of subjects in secluded, protected environments) a minimal requirement.

Rather than focussing on how little Mg can be tolerated, it is preferable to determine how much Mg can be taken without producing discomfort or adverse reactions. The widespread use of high dosage Mg as a cathartic, of lower (but still high) dosage as an antacid, and of pharmacologic Mg-dosage as an anticonvulsant and anti-hypertensive agent (e. g., in eclampsia), has provided us with toxicological data as to upper limits of safety. Unless there is renal immaturity (as in newborn infants) or renal decompensation, high intakes of Mg have proven safe. In contrast, Mg-deficiency has been associated with a vast array of experimental and clinical dysfunctions and diseases of varying severity. Geographic differences in incidences of diseases with manifestation in common with some produced by Mg-deficiency in animals (Reviews: [7, 158, 197, 270, 271, 274]) suggest possible interactions among host, environmental, and dietary factors that affect Mg-requirements, retention and distribution.

Might the adaptation of weanling rats to sustained low Mg-intakes, with long-term disadvantages in terms of tolerance to stress and life expectancy [133] be an experimental analogue of human sub-optimal Mg intakes from infancy onward, that might be contributory to many chronic diseases, and even to sudden cardiac death [268, 270—274, 278]? To what extent do nutritional imbalances that increase Mg-requirements, and genetic or physiologic differences, determine whether an individual will develop disorders against which increasing the Mg-intake might be protective? We must consider the implications of the early metabolic balance studies of pregnant women, which show that women on Mg-intakes in excess of the

RDA of 450 mg were in strongly positive Mg-balance during the third trimester [141, 164], in light of the surveys showing that pregnant middleclass American women ingest less Mg than half the RDA [14, 155]. To what extent does the developing human fetus suffer from a deficit that in experimental animals causes malformations, anemia, growth retardation, and edema [46, 55, 146, 147, 328], abnormalities depending on the time during gestation, and the degree of deficiency? Might gestational Mg deficiency (alone and in combination with other dietary imbalances) contribute both to maternal complications and to cardiovascular, skeletal and renal abnormalities, present at birth or becoming manifest later [267, 271, 272, 274]? Do infants born to mothers whose Mg-intakes are low or suboptimal, especially if their needs are high (as with teen-aged mothers and those with multiple or frequent births or who are diabetics, have higher Mg-requirements than can be met by milk: mother's or formula? This is a matter or urgent concern, in view of the recent conclusion that, because infant formulas provide 50—70 mg Mg/day, that is the requirement [101, 301]. Breast-fed infants are less subject to hypomagnesemic hypocalcemia than are formula-fed babies, a possible reflection of nutrient interactions (high Ca, P, and vitamin D content of cow's milk) that increase Mg-requirements [271, 272]. How much Mg is necessary to maintain positive Mg-balances by growing children? Adolescent boys required 10 to 16 mg/kg/day to allow for retention of enough Mg, realitive to N, to meet needs for growth and developments [263]. It may well be that pregnant and lactating women, athletes-in-training and competition, and convalescents have comparably high Mg-needs. The Mg provided in the diet or by supplements to adults in stable physical condition should be sufficient to allow for the extra needs under conditions of unexpected stress, and to meet the needs of those who have higher than average maintenance Mg-requirements. Little is known of the Mg-needs of those undergoing catabolic processes, as during chronic disease or in old age. Their low dietary supply of Mg [312], and the evidence of decreased Mg-absorption [154, 216[suggest that they are likely to be in Mg-deficit. Since nutrition influences the immunologic response to infection [43], and Mg plays an important role in humoral and cellular responses ([6, 69, 83, 165, 192, 241] Reviews: [270, 274]), the Mg-requirements of patients with infections might be elevated. Differences in plasma and erythrocyte Mg levels in groups with high predisposition to auto-immune diseases [130] suggest that they may have different Mg-requirements.

Also requiring study is the effect of dietary imbalances on Mg requirements. In the developed world, the common imbalances predisposing to Mg deficiency are predominantly caused by excesses: of vitamin D, phosphate and calcium, and of fat, protein and sugar. It is possible that megavitamin or trace mineral therapy might also adversely affect the retention of Mg. Metabolic abnormalities in utilization of vitamins and minerals that interact with Mg, and that might increase its requirements might also be contributory. Also affecting how much Mg is needed by the individual is efficacy of absorption and of renal tubular reabsorption of Mg. Since there are extremes of (Mg) malabsorption or renal wastage, it seems plausible that there might be less severe failures of Mg-utilization — whether genetically determined or produced by disease or dietary factors. It is quite possible that Mg-needs differ at extremes of altitude and climate, since plasma and erythrocyte Mg-levels differ [59, 131, 132]. Long-term balance studies are needed to ascertain how much Mg is needed to maintain equilibrium after the positive balances produced by supplements that bring the intake up to 6—10 mg/kg/day in stable adults, and after the larger amounts in those with the greater requirements of anabolism and stress.

Why has Mg been so neglected by so many in the medical community? Methodological difficulties have hampered accumulation of baseline data. There is disagreement, even among experts, as to what normal plasma Mg levels are [5, 319, 320, 326]. Wide ranges are accepted as normal [309], despite evidence that plasma Mg is normally maintained within narrow limits, that it is a poor index of the body Mg-status, and that narrow ranges should be determined for each laboratory [144, 223, 276, 326]. Renal Mg-retention of a parenteral Mg-load provides a better clue [35, 37—39, 58, 91, 193, 302, 335], but there are praktical drawbacks to this procedure, except in hospitals. Metabolic balance studies are important in establishing minimal needs, but this procedure is far too cumbersome and expensive to be directly applicable to the individual patient. Mg, being a major intracellular cation, determination of cellular Mg-levels should provide the best clue as to the adequacy of Mg in the body. Muscle and erythrocyte Mg-determinations have provided useful data [64, 69, 74, 77, 130—132, 179, 252, 326], but lags before deficiencies are reflected by changes in these tissues have limited applicability to a dynamic situation. Mg levels of mixed leukocytes [21, 22, 250] or of lymphocytes [50, 251, 286] might prove to be most reliable indicator of Mg levels in heart and other internal organs.

Until we can define, more precisely, how much Mg is needed for health — maintance at different ages and under different physiologic, pathologic, dietary, and environmental conditions, it is better to provide more than less Mg. For maintenance in the adult, not less than 6 mg/kg/day for women, and 7—10 mg/kg/day for men is likely to provide a margin of safety, that will meet needs even under conditions of increased requirements. For new tissue formation and repair, higher intakes are desirable, probably to 15 mg/kg/day and possibly more. Whether increasing the Mg-intake of humans might reduce the incidence and severity of dieseases with characteristics like those seen in experimental Mg-deficiency is a provocative possibility.

References

[1] *Achari, G., Mishra, K. C., Achari, K., Ramkissun, R., Upadhyay, S. N.:* J. Indian Med. Assoc. **36**: 93—95 (1961).
[2] *Aikawa, J. K.:* Proc. Soc. Exp. Biol. Med. **103**: 363—366 (1960).
[3] —*:* Proc. Spc. Exp. Biol. Med. **104**: 461—463 (1960).
[4] *Alcantara, E. N.:* Ph. D. Thesis, Univ. of Wisconsin (1970).
[5] *Alcock, N. W., MacIntyre, I., Radde, I.:* Nature **205**: 89—90 (1965).
[6] *Alcock, N. W., Shils, M. E.:* Proc. Soc. Exp. Biol. Med. **145**: 855—858 (1974).
[7] *Aleksandrowicz, J.:* In Protection of Man's Environment, Pol. Sc. Publ., p. 518—528 (1973).
[8] Am. Heart Assoc.: Circulation **58**: 762A—766A (1978).
[9] Am. Med. Assoc. Council on Sci. Aff.: J. A. M. A. **242**: 2335—2338 (1979).
[10] *Anderson, T. W., Leriche, W. H., Hewitt, D., Neri, L. C.:* In Cantin, M., Seelig, M. S. (eds). Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 565—571 (1980). Proc. 2nd Int'l. Mg. Sympos. (Montreal, Canada (1976).
[11] *Anderson, T. W., Neri, L. C., Schreiber, G. B., Talbot, F. D. F., Zdrojewski, A.:* Can. Med. Assoc. Med. J. **113**: 109—113 (1975).
[12] *Anghileri, L. J., Heidbreder, M.:* Europ. J. Cancer **13**: 291—292 (1977).
[13] *Anghileri, L. J., Heidbreder, M., Weiler, G., Dermietzel, R.:* Exp. Cell Biol. **45**: 34—47 (1977).
[14] *Ashe, J. R., Scofield, F. A., Gram, M. R.:* Am. J. Clin. Nutr. **32**: 281—286 (1979).
[15] *Aurousseau, M., Larvor, P., Durlach, J.:* Proc. 1st Mg. Congress, Argentina (1968).
[16] *Bajusz, E.:* Nutritional Aspects of Cardiovascular Diseases. J. B. Lippincott Philadelphia and Montreal (1965).
[17] *Bajusz, E., Selye, H.:* Trans. N. Y. Acad. Sci. **21**: 659—667 (1959).
[18] *Bawkin, H.:* J. Pediat. **14**: 1—10 (1939).
[19] *Barker, E. S., Elkinton, J. R., Clark, J. K.:* J. Clin. Inv. **38**: 1733—1745 (1959).
[20] *Barnes, B. A., Cope, O., Harrison, T.:* J. Clin. Inv. **37**: 430—440 (1958).
[21] *Baron, D. N.:* Proc. Roy. Soc. Med. **62**: 945—953 (1969).
[22] *Baron, D. N., Ahmed, S. A.:* Clin. Sci. **37**: 205—219 (1969).
[23] *Baumslag, N., Yeager, D., Levin, L., Petering, H. G.:* Arch. Env. Health. **29**: 186—191 (1974).
[24] *Beisel, W. R.:* Am. J. Clin. Nutr. **32**: 271—274 (1979).
[25] *Bessey, O. A., Adams, D. J. D., Hansen, A. K.:* Pediatrics **20**: 33—44 (1957).
[26] *Better, O. S., Massry, S. G.:* J. Lab. Clin. Med. 79: 794—800 (1972).
[27] *Blaxter, K. L., Wood, W. A.:* Brit. J. Nutr. **6**: 144—163 (1952).
[28] *Bodansky, M.:* Am. J. Clin. Path. 9: 36—51 (1939).
[29] *Bogert, L. J., Trail, R. L.:* J. Biol. Chem. **54**: 753—761 (1922).
[30] *Boullin, D. J.:* J. Physiol. **189**: 85—99 (1967).
[31] *Brin, M.:* Am. K. Clin. Nutr. **24**: 704—798 (1971).
[32] *Bunce, G. E., Sauberlich, H. E., Reeves, P. G.:* J. Nutr. **86**: 406—414 (1965).
[33] *Caddell, J. L.:* Ann. N. Y. Acad. Sci. **162**: 874—890 (1969).
[34] —*:* Pediatrics **66**: 392—413 (1965).
[35] —*:* Clin. Pediatr. **14**: 449—459, 518—519 (1975).
[36] *Caddell, J. L., Olson, R. E.:* J. Pediatr. **83**: 124—128 (1973).
[37] *Caddell, J. L., Ratananon, N., Trangratapit, P.:* Am. J. Clin. Nutr. **26**: 612—615 (1973).
[38] *Caddell, J. L., Saier, F. L., Thomason, C. A.:* Am. J. Clin. Nutr. **28**: 1099—1104 (1975).
[39] *Caddell, J. L., Suskind, R., Sillup, H., Olson, R. E.:* J. Pediatr. **83**: 129—135 (1973).
[40] *Campbell, B. J., Reinhold, J. G., Cannell, J. J., Nourmand, I.:* Pahlavi Med. J. 7: 1—17 (1976).
[41] *Cantin, M.:* Lab. Invest. **22**: 558—568 (1970).
[42] *Chan, G. M., Tsang, R. C., Chen, I. W., Deluca, H. F., Steichen, J. J.:* J. Pediat. 93: 91—96 (1978).
[43] *Chandra, R. K., Newberne, P. M.:* Nutrition, Immunity and Infection. Plenum Medical Book Co., New York (1977).
[44] *Clark, G. M.:* Univ. Calif. Publ. in Physiol. **5**: 195—287 (1926).
[45] *Cockburn, F., Brown, J. K., Belton, N. R., Forfar, J. O.:* Arch. Dis. Childh. **48**: 99—108 (1973).
[46] *Cohlan, S. Q., Jansen, V., Dancis, J., Piomelli, S.:* Blood **36**: 500—506 (1970).
[47] *Consolazio, C. F., Matoush, L. O., Johnson, H. L., Nelson, R. A., Krzywick, H. J.:* Am. J. Clin. Nutr. **20**: 672—683 (1967).
[48] *Coons, C. M., Schiefelbusch, A., Marshall, G. B., Coons, R.:* Exp. Sta. Bull. # 223 U. S. Dept. Agric. (1935).
[49] *Cooper, J. R., Itokawa, Y., Pincus, J. H.:* Science **164**: 74—75 (1969).
[50] *Counihan, T. B., Halley, E., Ryan, M. F., Ryan, M. P.:* Irish J. Med. Sci. **147**: 327, 331—332 (1978).
[51] *Crawford, T., Crawford, M. D.:* Lancet **1**: 229—232 (1967).
[52] *Cubberley, P. T., Polster, S. A., Schulman, C. L.:* New Engl. J. Med. **272**: 628—630 (1965).
[53] *Cullumbine, H., Basnayake, V., Lemottee, J., Wickramanayake, T. W.:* Brit. J. Nutr. **4**: 101—111 (1950).
[54] *Cushard, W. G., Jr., Creditor, M. A., Canterbury, J. M., Reiss, E.:* J. Clin. Endocr. Metab. **34**: 767—771 (1972).
[55] *Dancis, J., Springer, D., Cohlan, S. O.:* Pediatr. Res. **5**: 131—136 (1971).
[56] *Daniels, A. L.:* Am. J. Dis. Child. **62**: 568—576 (1941).
[57] *Daniels, A. L., Everson, G. J.:* J. Nutr. **11**: 327—341 (1936).
[58] *Danielson, B. G., Johansson, G., Ljunghall, S.:* In Johansson, G. (ed). Magnesium Metabolism, Ed. G. Johansson, Publ. Almqvist & Wiksell, Stockholm, Sweden 1979: II: 1—25.
[59] *Darlu, P.:* Intl. J. Biometeor. 19: 166—173 (1975).
[60] *Davis, J. A., Harvey, D. R., YU, J. S.:* Arch. Dis. Childh. **40**: 286—290 1965.
[61] *De Jorge, B. F. B., Delascio, D., Barros de Ulhoa, Cintra, A., Antunes, M. L.:* Obst. Gynec. **25**: 253—254 (1965).
[62] *Douglas, W. W., Rubin, R. P.:* J. Physiol. **175**: 231—241 (1964).
[63] *Draper, H. H.:* J. Nutr. **83**: 65—72 (1964).
[64] *Drenick, E. J., Brickman, A. S.:* In *Durlach, J.* (ed.) Proc. 1st Int'l. Sympos. on Mg, Vittel, France, 1971, p. 491—498 (1973).
[65] *Drenick, E. J., Hunt, I. F., Swendseind, M. E.:* Clin. Endocr. Metab. **29**: 1341—1348 (1969).
[66] *Drews, L. M., Kies, C., Fox, H. M.:* Am. J. Clin. Nutr. **32**: 1893—1897 (1979).
[67] *Duckworth, J., Warnock, G. M.:* Nutr. Abstr. Rev. **12**: 167—183 (1942).
[68] *Dull, T.:* Clin. Res. **11**: 404—405 (1963).
[69] *Durlach, J.:* In Cantin, M., & M. S. Seelig, Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 883—909 (1980). Proc. 2nd Intl. Mg Sympos., Montreal, Canada (1976).
[70] —*:* Vie Med. **41**: 966—969 (1960).

[71] —: Nouv. Arch. Hosp. 42: 31—40 (1970).
[72] —: Diabete 19: 99—113 (1971).
[73] —: In: *Vinken, P. J. Bruyn, G. W.* (eds), Handbook of Clinical Neurology **28**, North-Holland Publ. Co., Amsterdam-Oxford-New York, p. 545—579 (1976).
[74] —: Spasmophilia and Magnesium Deficit. Masson Co., Paris, France, p. 63—136 (1969).
[75] *Durlach, J., Lebrun, R.:* Ann. Endocr. (Paris) **21**: 244—252 (1960).
[76] *Durlach, J., Rayssiguier, Y., Laguitton, A.:* Med. Nutr. **16**: 15—21 (1980).
[77] *Dyckner, T., Wester, P. O.:* In: *Cantin, M., Seelig, M. S.,* Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 551—557 (1980). Proc. 2nd Intl. Mg Sympos., Montreal, Canada (1976).
[78] *Ebadi, M. S., Bostad, R., Pellegrino, R. J.:* J. Neur., Neurosurg., Psychiatr. 32: 393—398 (1969).
[79] *Ebel, H., Gunther, T.:* J. Clin. Chem. Clin. Biochem. **18**: 257—270 (1980).
[80] *Ebels, E. J., Blokzijl, E. J., Troelstra, J. A.:* Helv. Paed. 3: 310—324 (1965).
[81] *Elin, R. J.:* Proc. Soc. Exp. Biol. Med. **142**: 1159—1161 (1973).
[82] —: In: *Cantin, M., Seelig, M. S.,* Magnesium in Health and Disease. SP Medical & Scientific Books, Jamaica, New York, p. 113—124 (1980). Proc. 2nd Intl. Mg. Sympos. Montreal, Canada (1976).
[83] —: Proc. Soc. Exp. Biol. Med. **148**: 620—624 (1975).
[84] *Elin, R. J., Tan, H. K.:* Blood 49: 657—664 (1977).
[85] *Ertel, N. H., Reiss, J. S., Spergel, G.:* New Engl. J. Med. **280**: 260—262 (1969).
[86] *Feenstra, L., Wilkens, J. H.:* Ned. T. Geneesk **109**: 615—19 (1965).
[87] *Fehlinger, R.:* Rev. Franc. Endocr. Clin. Nutr. Metab. **20**: 501—513 (1979).
[88] —: Magnesium Bull. 2: 40—47 (1980).
[89] *Feigin, I., Wolf, A.:* J. Pediatr. **45**: 243—263 (1954).
[90] *Fenn, W. O., Goetisch, M.:* J. Biol. Chem. **120**: 41—51 (1937).
[91] *Fitzgerald, M. G., Fourman, P.:* Clin. Sci. **15**: 635—647 (1956).
[92] *Flink, E. B.:* In: *Cantin, M., Seelig, M. S.:* Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 865—882 (1980). Proc. 2nd Intl. Mg. Sympos. Montreal, Canada (1976).
[93] *Flink, E. B., Flink, P. F., Shane, S. R., Jones, J. E., Steffes, P. E.:* Clin. Res. **21**: 884 (1973).
[94] *Flink, E. B., McCollister, R., Prasad, A. S., Melby, J. C., Doe, R. P.:* Ann. Intern. Med. 47: 956—968 (1957).
[95] *Flink, E. B., Morano, G. D., Morabito, R. A., Shane, S. R., Scobbo, R. R.:* In: *Cantin, M., Seelig, M. S.* (eds). Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 73—78 (1980). Proc. 2nd Intl. Mg Sympos., Montreal, Canada (1976).
[96] *Flink, E. B., Shane, S. R., Scobbo, R. R., Blehschmidt, N. G., McDowell, P.:* Metabolism **28**: 858—865 (1979).
[97] *Flink, E. B., Stutzman, F. L., Anderson, A. R., Konig, T., Fraser, R.:* J. Lab. Clin. Med. 43: 169—183 (1954).
[98] *Flowers, C. E.* jr.: Am. J. Obst. Gyn. **91**: 763—776 (1965).
[99] *Fodor, J. G., Pfeiffer, C. J., Papezik, V. S.:* Can. Med. Assoc. J. **108**: 1369—1373 (1973).
[100] *Food* & Nutr. Board, Nat'l Res. Council: Publ. Natl. Acad. Sci. Washington, D. C. Intl. Standard # 0-309-00377-3 (1980).
[101] *Food* & Nutr. Board, Nat'l Res. Council: Recommended Dietary Allowances. Ed. 9, Natl. Acad. Sci., Washington, D. C. (1980).
[102] *Forbes, R. M.:* J. Nutr. **80**: 321—326 (1963).
[103] *Fourman, P., Morgan, D. B.:* Proc. Nutr. Soc. **21**: 34—41 (1962).
[104] *Freeman, R. M., Pearson, E.:* Am. J. Med. **41**: 645—656 (1966).
[105] *Friderichsen, C.:* Lancet 1/6: 85—86 (1939).
[106] *Frimpter, G. W., Andelman, R., George, W. F.:* Am. J. Clin. Nutr. 22: 794—803 (1969).
[107] *Garnett, E. S., Barnard, D. L., Ford, J., Goodbody, R. A., Woodehouse, M. A.:* Lancet 1: 914—916 (1969).
[108] *Gershoff, S. N.:* Proc. Soc. Exp. Biol. Med. **127**: 1207—1210 (1968).
[109] *Gershoff, S. N., Prien, E. L.:* Am. J. Clin. Nutr. **20**: 393—399, 1967.
[110] *Gitelman, H. J., Graham, J. B., Welt, L. G.:* Ann. N. Y. Acad. Sci. **162**: 856—864 (1969).
[111] *Gittleman, I. F., Pincus, J. B., Schmertzler, E.:* Am. J. Dis. Child. **107**: 119—124 (1964).
[112] *Goldsmith, L. A.:* J. Nutr. 93: 87—102 (1967).
[113] *Gormican, A., Catli, E.:* Nutr. Metab. **13**: 364—377 (1971).
[114] *Greenberg, D. M.:* Biochem. **8**: 269—300, 1939.
[115] *Greenberg, D. M., Tufts, E. V.:* Am. J. Physiol. **121**: 416—423 (1938).
[116] *Greger, J. L., Bennett, O. A., Abernathy, R. P.:* Fed. Proc. **36**: 1130 (1977).
[117] *Greger, J. L., Baligar, R., Abernathy, R. P., Bennett, O. A., Peterson, T.:* Am. J. Clin. Nutr. **31**: 117—121 (1978).
[118] *Greger, J. L., Gruner, S. M., Ethyre, G. M., Abernathy, R. P., Sickles, V.:* Nutr. Rep. Int'l. **20**: 235—243 (1979).
[119] *Greger, J. L., Huffman, J., Abernathy, R. P., Bennett, O. A., Resneck, S. E.:* J. Food Sc. 44: 1765, 1766, 1771 (1979).
[120] *Haijamae, H., MacDowell, I. G.:* Acta Paediatr. Scand. **61**: 591—596 (1972).
[121] *Hall, D. G.:* Obst. Gyn. 9: 158—162 (1957).
[122] *Hambidge, K. M., Walravens, P. A.:* In Prasad, A. S., Trace Elements in Human Health and Disease **1**, Academic Press, New York, p. 21—32 (1976).
[123] *Harrington, D. D.:* Brit. J. Nutr. 34: 45—57 (1975).
[124] *Hartenstein, H., Gardner, L. I.:* New Engl. J. Med. 274: 266—268 (1966).
[125] *Hathaway, M. L.:* Home Econ. Res. Report # 19, Agric. Res. Serv. U. S. D. A. Washington, D. C. (1962).
[126] *Haury, V. G., Cantarow, A.:* J. Lab. Clin. Med. 27: 616—622 (1942).
[127] *Haywood, J., Selvester, R.:* Clin. Med. **10**: 87 (1962).
[128] *Heaton, F. W.:* In Cantin, M., & Seelig, M. S., Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, 43—55 (1980). Proc. 2nd Int'l. Mg Sympos. Montreal, Canada (1976).
[129] *Hellerstein, E. E., Nakamura, M., Hegsted, D. M., Vitale, J. J.:* J. Nutr. 71: 339—346 (1960).
[130] *Henrotte, J. G.:* C. R. Acad. Sc. (Paris) **285**: 737—739 (1977).
[131] *Henrotte, J. G., Benech, A., Pineau, M.:* In: *Cantin, M., Seelig, M. S.* Magnesium in Health and Disease, SP Medical & Scientific Booksm Jamaica, New York, p. 929—934 (1980). Proc. 2nd Int'l Mg Sympos., Montreal, Canada (1976).
[132] *Henrotte, J. G., Pechery, C., Durlach, J., De Traverse, P. M.:* In: *Durlach, J.* (ed.) Proc. 1st Int'l Mg Sympos. 1971, Vittel, France 2, p. 573—576 (1973).
[133] *Heroux, O., Peter, D., Heggtveit, A.:* J. Nutr. **107**: 1640—1652 (1977).
[134] *Hills, A. G., Parsons, D. W., Webster, G. D., Rosenthal, O.:* J. Clin. Endocr. Metab. **19**: 1192—1211 (1959).
[135] *Hodgkinson, A., Heaton, F. W.:* Clin. Chim. Acta **11**: 354—362 (1965).
[136] *Hoffstrom, K. A.:* Skand. Arch. Physiol. 23: 326—420 (1916).
[137] *Holtmeier, H. J.:* In: *Heilmeyer, L.* (ed.) Ernährungswis-

senschaften, V. Sympos. Freiburg, 1967, George Thieme Verlag, Stuttgart, W. Germany, p. 111—152 (1968).
[138] —: In: *Durlach, J.* (ed.) Proc. 1st Int'l Mg Sympos., 1971, Vittel, France **1**, p. 397—417 (1971).
[139] *hsu J. M.:* Proc. Soc. Exp. Biol. Med. 119: 177—180 (1965).
[140] *Hummel, F. C., Hunscher, H. A., Bates, M. F., Bonner, P., Macy, I. G.:* J. Nutr. 13: 263—278 (1937).
[141] *Hummel, F. C., Sternberger, H. R., Hunscher, H. A., Macy, I. G.:* J. Nutr. 11: 235—255 (1936).
[142] *Hungerford, G. F., Bernick, S.:* In: *Cantin, M., Seelig, M. S.,* Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 659—670 (1980). Proc. 2nd Int'l. Mg. Sympos., Montreal, Canada (1976).
[143] *Hunscher, H. A.:* J. Am. Diet. Assoc. 39: 209—219 (1961).
[144] *Hunt, B. J.:* Clin. Chem. 15: 979—996 (1969).
[145] *Hunt, S. M., Schofield, F. A.:* Am. J. Clin. Nutr. 22: 367—373 (1969).
[146] *Hurley, L. S.:* In: *Durlach, J.* (ed.) Proc. 1st Int'l Mg. Sympos., Vittel, France, p. 481—492 (1971).
[147] *Hurley, L. S., Cosens, G., Therrault, L. L.:* J. Nutr. **106**: 1254—1260 (1976).
[148] *Irwin, M. I., Feeley, R. M.:* Am. J. Clin. Nutr. 20: 816—824 (1967).
[149] *Irwin, M. I.* & Wiese, H. F.: J. Nutr. 74: 217—225 (1961).
[150] *Itokawa, Y., Inoue, K., Natori, Y., Okazaki, K., Fujiwara, M.:* J. Vitaminol. **18**: 159—164 (1972).
[151] *Itokawa, Y., Tanaka, C., Kimura, M.:* Metabolism 21: 371—375 (1972).
[152] *Itokawa, Y., Tseng, L. F., Fujiwara, M.:* J. Nutr. Sci. Vitaminol. 20: 249—255 (1974).
[153] *Jabir, F. K., Roberts, S. D., Womersley, R. A.:* Clin. Sci. 16: 119—124 (1957).
[154] *Johansson, G.:* Scand. J. Urol. Nephrol. Suppl. **51**: 1—16 (1979).
[155] *Johnson, N. E., Philipps, C.:* In: *Cantin, M., Seelig, M. S.,* Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 827—831 (1980). Proc. 2nd Int'l Mg. Sympos. Montreal, Canada, 1976.
[156] *Jones, J. E., Shane, S. R., Jacobs, W. H., Flink, E. B.:* Ann. N. Y. Acad. Sci. 162: 934—946 (1969).
[157] *Kalbfleisch, J. M., Lindeman, R. D., Smith, W. O.:* J. Lab. Clin. Med. 48: 833—834 (1961).
[158] *Karppanen, H., Pennanen, R., Passinen, L.:* Adv. Cardiol. 25: 9—24 (1978).
[159] *Keating, F. R., jr., Jones, J. D., Elveback, L. R., Randall, R. T.:* J. lab. Clin. Med. 73: 825—834 (1969).
[160] *Kelsay, J. L., Behall, K. M., Prather, E. S.:* Am. J. Clin. Nutr. 32: 1876—1880 (1979).
[161] *Knochel, J. P.:* Arch. Int. Med. 137: 203—220 (1977).
[162] *Korbitz, B. C.:* J. Vitaminol. 16: 137—139 (1970).
[163] *Landes, R. R., Melnick, I., Sierakowski, R., Finlayson, B.:* In Seelig, M. S. (ed.), Nutritional Imbalances in Infant and Adult Diseases, SP Medical & Scientific Books, Jamaica, New York, p. 9—21 (1977).
[164] *Landsberg, E.:* Zschr. Geburts. Gyn. 75: 53—98 (1914).
[165] *Larvor, P.:* In *Cantin, M* & *Seelig, M. S.,* Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 201—224 (1980). Proc. 2nd Int'l Mg Sympos., 1976, Montreal, Canada.
[166] *Larvor, P., Durlach, J.:* Vie Med. 35: 4359—4368 (1973).
[167] *Lazard, E. M.:* Am. J. Obst. Gyn. 9: 178—188 (1925).
[168] *Lebenthal, E.:* In: *Lifshitz, F.* (ed.) Clinical Disorders in Pediatric Nutrition, Marcel Dekker Press, New York (in press, 1981).
[169] *Lehr, D.:* In Bajusz, E. (ed.) Electrolytes and Cardiovascular Diseases 1, S. Karger, Basel/New York, p. 248—273 (1965).
[170] —: Ann. N. Y. Acad. Sci. 156. 344—378 (1969).
[171] *Lehr, D., Chau, R., Kaplan, J.:* In Bajusz, E & Rona, G. (eds.). Recent Advances in Cardiac structure and Metabolism, I. Myocardiology, University Park Press, Baltimore, p. 684—698 (1972).
[172] *Leitch, I., Hepburn, A.:* Nutr. Abstr. Rev. 31, 389—401 (1961).
[173] *Lemann, J., Lennon, E. J., Piering, W. R., Prien, E. L., Ricanati, E. S.:* J. Lab. Clin. Med. 75, 578—585 (1970).
[174] *Lemann, J.; Piering, W. F., Lennon, E. J.:* J. Lab. Clin. Med. 70, 987—988 (1967).
[175] *Lemann, J., Piering, W. F., Lennon, E. J.:* J. Lab. Clin. Med. 70: 987—988 (1967).
[175] *Lennon, E. J.:* In Seelig, M. S. (ed.), *Nutritional Imbalances in Infant and Adult Diseases,* SP Medical & Scientific books, Jamaica, New York, p. 127—139 (1977).
[176] *Lennon, E. J., Lemann, J. Jr., Piering, W. E., Larson, L. S.:* J. Clin. Inv. 53, 1424—1433 (1974).
[177] *Leveille, G. A.:* Dietary fiber. Food & Nutr. News 47: (1976).
[178] *Lieber, I. I.:* Prensa Med. Argentina 48: 44—52 (1961).
[179] *Lim, P., Jacob, E., Dong, S., Khoo, O. T.:* J. Clin. Path. 22: 417—421 (1969).
[180] *Lindeman, R. D.:* In: *Cantin, M., Seelig, M. S.,* (eds.). Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 381—399 (1980). Proc. 2nd Int'l Mg. Sympos., 1976, Montreal, Canada.
[181] *Lindeman, R. D., Adler, S., Yiengst, M. J., Beard, E. S.:* J. Lab. Clin. Med. 70, 236—245 (1967).
[182] *Linden, V.:* In Seelig, M. S. (ed.) Nutritional Imbalances in Infant and Adult Diseases, SP Medical & Scientific Books, Jamaica, New York, p. 23—42 (1977).
[183] *Linden, V.:* Brit. Med. J. 3, 647—750 (1974).
[184] *Lowe, C. U.:* Am. J. Clin. Nutr. 25, 245—254 (1972).
[185] *Lutwak, L., Singer, F. R., Urist, M. R.:* Ann. Intern. Med. 80: 630—644 (1974).
[186] *McCance, R. A., Widdowson, E. M.:* J. Physiuol. 101, 44—85 (1942).
[187] —, —: J. Physiol. 101, 304—313 (1942).
[188] *McCance, R. A., Widdowson, E. M., Lehmann, H..* Biochem. J. 36, 686—691 (1942).
[189] *McCance, R. A., Widdowson, E. M.:* Brit. Med. Bull, 17, 132—136 (1961).
[190] *McCollister, R. J., Flink, E. B., Lewis, M. D.:* J. Clin. Nutr. 12, 415—420 (1963).
[191] *Mc Cormick, D. B., Gregory, M. E., Snell, E. E.:* J. Biol. Chem. 236, 2076—2084 (1961).
[192] *McCoy, J. H., Kenney, M. A.:* J. Nutr. 105, 791—797 (1975).
[193] *McDonald, J. T., Margen, S.:* Am. J. Clin. Nutr. 32, 823—833 (1979).
[194] *McHale, M., Kies, C., Fox, H. M.:* j. Food Sci. 44, 1412—1417 (1979).
[195] *McKey, B. V., LaFont, F. M., Borchers, G. L., Navarrete, D. A., Holmes, J. O.:* Fed. Proc. 21, 310 (1962).
[196] *Macy, I. G.:* Nutrition & Chemical Growth in Childhood, III. Charles C. Thomas, Springfield, III, 1951.
[197] *Marier, J. R.:* Rev. Can. Biol. 37, 115—125 (1978).
[198] *Marsh, A. G., Ford, D. C., Christensen, D. K.:* J. Am. Diet. Assoc. 51, 441—446 (1967).
[199] *Marshall, D. H., Nordin, B. E. C., Speed, R.:* Proc. Nutr. Soc. 35, 163—173 (1976).
[200] *Marshall, M. W., Iacono, J. M., Young, C. W., Washington, V. A., Slover, H. T., Leapley, P. M.:* J. Am Diet. Assoc. 66, 470—481 (1975).
[201] *Martin, H. E.:* Ann. N. Y. Acad. Sci. 162, 891—900 (1969).
[202] *Martin, J. E., Jones, R.:* Am. Heart J. 62, 206—210 (1961).
[203] *Maynard, L.A., Boggs, D., Fisk, G., Seguin, D.:* J. Nutr. 64, 85—97 (1958).

[204] *Mays, E. T., Randall, H. T., Deweese, B. M.:* Surgery **67**, 780—788 (1970).
[205] *Mellinghoff, K.:* Dtsch. Arch. Klin. Med. **195**, 475—480 (1949).
[206] *Mellinghoff, K., An Lessen, W.:* Dtsch. Arch. Klin. Med. **194**, 285—293 (1949).
[207] *Melnick, I., Landes, R. R., Hoffman, A. A.:* In Durlach, J. (ed.) Proc. 1st Int'l Mg Sympos., Vittel, France, 1971, 2, p. 69—72 (1973).
[208] *Melnick, I., Landes, R. R., Hoffman, A. A., Burch, J. F.:* J. Urol. **105**, 119—122 (1971).
[209] *Michelis, M. F., Drash, A. L., Linarelli, L. G., Derubertis, F. R., Davis, B. B.:* Metabolism **21**, 905—920 (1972).
[210] *Michiel, R. R., Sneider, J. S., Dickstein, R. A., Hayman, H., Eich, R. H.:* New Engl. J. Med. **198**, 1005—1007 (1978).
[211] *Miller, R. T., Faloon, W. W., Lloyd, C. W..* J. Clin. Endocr. Metab. **18**, 1178—1185 (1958).
[212] *Mishra, K.:* Rev. Can. Biol. **19**, 143-153 (1960).
[213] *Monteleone, J. A., Lee, J. B., Tashjian, A. H., Cantor, H. E.:* Ann. Intern. Med. **82**, 670—672 (1975).
[214] *Morris, E. R., O'dell, B. L.:* J. Nutr. **75**, 77—85 (1961).
[215] —, —: J. Nutr. **81**, 175—181 (1963).
[216] *Mountokalakis, Th., Singhellakis, P. N., Alevizaki, C. C., Caramanakos, E., Ikkos, D. G.:* Rev. Franc. Endocr. Clin. Nutr. Metab. **17**, 229—232 (1976).
[217] *Munoz, J. M., Sandstead, H. H., Jacob, R. A., Logan, G. M. Jr, Reck, S. J., Klevay, L. M., Dintzis, F. R., Inglett, G. E., Shuey, W. C.:* Am. J. Clin. Nutr. **32**, 580—592 (1979).
[218] *Nabarro, D. N., Spencer, A. G., Stowers, J. M.:* Quart. J. Med. **21**, 225—243 (1952).
[219] *Neri, L. C., Hewitt, D., Schreiber, G. B., Anderson, T. W., Mandel, J. S., Zdrojewsky, A.:* J. A. W. W. A. **67**, 403—409 (1975).
[220] *Neri, L. C., Marier, J. R.: In: Naito, H. K., Gerrity, R. G. (eds.),* Nutrition and Cardiovascular Diseases, SP Medical & Scientific Books, Jamaica, New York (in press.).
[221] *Newman, R. L.:* Obst. Gyn. **10**: 51—55 (1957).
[222] *Nordio, S., Donath, A., Macagno, F., Gatti, R.:* Acta Paediat. Scand. **60**: 441—448, 449—455 (1971).
[223] *Nuoranne, P.:* Nord. Vet. Med. **30**: 71—73 (1978).
[224] *Nuoranne, P., Raunio, R. P., Saukko, P., Karppanen, H.:* Brit. J. Nutr. **44**: 53—60 (1980).
[225] *O'Dell, B. L., Morris, E. R., Regan, W. O.:* J. Nutr. **70**: 103—110 (1960).
[226] *Parsons, R. S.:* Med. J. Austral. **1**: 883—884 (1958).
[227] *Paunier, L.:* Med. Nutr. **16**: 31—36 (1980).
[228] *Paunier, L., Radde, I. C., Kooh, S. W.:* Pediatrics **41**: 385—402 (1968).
[229] *Paunier, L., Sizonenko, P. C.:* J. Pediatr. **88**: 51—55 (1976).
[230] *Petersen, V. P.:* Acta Med. Scand. **173**: 285—298 (1963).
[231] *Petrunkina, A.:* Ztschr. Kinderheilk. **56**: 219—226 (1934).
[232] *Prasad, A. S.:* Zinc in Human Nutrition, CRC Press, Boca Raton, Fl. 1979.
[233] *Prein, E. L.:* J. A. M. A. **19**: 177 (1965).
[234] *Pritchard, J. A., Stone, S. R.:* Am. J. Obst. Gynec. **99**: 752—765 (1967).
[235] *Raab, W.:* In *Bajusz, E.* & *Rona, G.* (eds.) Recent Advances in Studies on Cardiac Structure and Metabolism, I. Myocardiology, University Park Press, Baltimore, p. 707—713 (1972).
[236] *Raab, W.:* Ann. N. Y. Acad. Sci. **147**: 627—686 (1969).
[237] *Rapado, A., Castrillo, J. M.:* In: *Cantin, M., Seelig, M. S.* (eds.)., Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, N. Y., p. 355—364 (1980). Proc., 2nd Intl Mg Symposium, 1976, Montreal, Canada.
[238] *Rapado, A., Castrillo, J. M.:* Ibid, p. 485—497 (1980).
[239] *Rayssiguier, Y.:* Horm. Metab. Res. **9**: 309—314 (1977).
[240] *Rayssiguier, Y., Gueux, E.:* Ann. Nutr. Aliment. **33**: 545—546 (1979).
[241] *Rayssiguier, Y., Larvor, P., Augusti, Y., Durlach, J.:* Ann. Biol. Anim. Bioch. Biophys. **17**: 147—152 (1977).
[242] *Rayssiguier, Y., Larvor, P.:* In: *Cantin, M., Seelig, M. S.* (eds.) Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, N. Y., p. 67—72 (1980), Proc. 2nd Intl Mg Sympos. 1976, Montreal, Canada.
[243] *Reinhold, J. G., Bahram, F., Parichehr, A., Ismall-Beigi, F.:* J. Nutr. **106**: 493—503 (1976).
[244] *Rigo, J.:* In: *Durlach, J.* (ed.) Proc. 1st Intl Mg Sympos., Vittel, France, p. 214—228 (1971).
[245] *Rigo, J.,* Gerontologia 2: 25—33 (1965).
[246] *Rigo, J., Li, B. N., Zelles, T., Szelenyi, I., Sos, J.:* Acta Physiol. Acad. Sci. Hung. Suppl. 25: 40 (1865).
[247] *Rigo, J., Simon, G., Hegyvari, C., Sos, J.:* Acta Med. Acad. Sci. Hung. **19**: 231—236 (1963).
[248] *Rigo, J., Szelenyi, I., Sos, J.:* Acta Physiol. Acad. Sc. Hung. 32: (Suppl.) 16 (1967).
[249] *Rosenbloom, A.:* Metabolism **26**: 1033—1039 (1977).
[250] *Ross, R. S., Seelig, M. S., Berger, A. R.:* In: *Cantin, M., Seelig, M. S.* (eds.). Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 7—15 (1980). Proc. 2nd Intl. Mg. Sympos., 1976, Montreal, Canada.
[251] *Ross, R. S., Seelig, M. S., Berger, A. R.* (this Symposium).
[252] *Rousselet, F., Durlach, J.:* In: *Durlach, J.,* Proc. 1st Int'l Mg. Sympos., Vittel, France, p. 65—90 (1971).
[253] *Rubin, H.:* Proc. Nat. Acad. Sci. USA 72: 3551—3555 (1975).
[254] *Rubin, R. P.:* Pharmacol. Rev. 22: 389—428 (1970).
[255] *Runeberg, L., Collan, Y., Jokinen, E. J., Lahdevirta, J., Aro, A.:* Am. J. Med. **59**: 873—991 (1975).
[256] *Salet, J., Polonovski, C., de Gouyon, F., Pean, G., Melekian, B., Fournet, J. P.:* Arch. Franc. Pediat. 23: 749—768 (1966).
[257] *Salet, J., Polonovski, C., Fournet, deGouyon, F., Aymard, P., Pean, G., Taillemite, J. L.:* Arch. Franc. Pediat. 27: 550—551 (1970).
[258] *Sandstead, H. H., Klevay, L. M., Jacob, R. A., Munoz, J. M., Logan, G. M., jr., Reck, S. J.:* In: *Inglett, G. E., Falkenhag, S. I.* (eds.) Dietary Fibers: Chemistry and Nutrition, Academic Press, New York, p. 147—156 (1979).
[259] *Savoie, L. L.:* Path. Biol. **20**: 19—20; 751—756 (1972).
[260] *Savoie, L. L., Delorme, B.:* In *Cantin, M.* & *Seelig, M. S.,* Magnesium in Health & Disease. SP Medical & Scientific Books, Jamaica, New York, p. 537—544 (1980). Proc. 2nd Int'l. Mg. Sympos. 1976, Montreal, Canada.
[261] *Sawyer, M., Baumann, L., Stevens, F.:* J. Biol. Chem. 33: 103—109 (1918).
[262] *Schlutz, F. W., Morse, M., Oldham, H.:* Am. J. Dis. Child. **46**: 757—774 (1933).
[263] *Schwartz, R., Walker, G., Linz, M. D., MacKellar, I.:* Am. J. Clin. Nutr. **26**: 510—518 (1973).
[264] *Schwartz, R., Woodcock, N. A., Blakeley, J. D., MacKellar, I.:* Am. J. Clin. Nutr. 26: 519—523 (1973).
[265] *Schwarz, K.:* In: *Harris, R. S., Wool, I. G.* (eds.) Vitamins and Hormones 20, Academic Press, New York, p. 463—484 (1962).
[266] *Scriver, C. R.:* Pediatrics **26**: 62—74 (1960).
[267] *Seelig, M. S.:* In: *Lavery, P. C.* (ed.) Nutrition in Pregnancy (in press, 1981).
[268] —: In: *Naito, H. K., Gerrity, R.* (eds.) Nutrition and Cardiovascular Diseases, SP Medical & Scientific Books, Jamaica, New York (in press, 1981).

[269] —: In: *Durlach, J.* (ed.), Proc. 1st Int'l Mg Sympos., Vittel, France, p. 11—38 (1971).
[270] —: Biol. Tr. Elem. Res. **1**: 273—297 (1979).
[271] —: Magnesium Deficiency in the Pathogenesis of Disease. Early Roots of Cardiovascular, Skeletal, and Renal Abnormalities. Ser. Ed., L. V. Avioli, Plenum Medical Books, New York (1980).
[272] —: Cardiovasc. Med. 3: 637—650 (1978).
[273] —: In: *Bajusz, E., Rona, G.* (eds.) Recent Advances in Studies on Cardiac Structure and Metabolism. I. Myocardiology, University Park Press, Baltimore, p. 615—625; 626—638 (1972).
[274] —: In: *Lifshitz, F.* (ed.) Clinical Disorders in Pediatric Nutrition, Marcel Dekker, New York (in press 1981).
[275] —: Am. J. Clin. Nutrition, **14**: 342—390 (1964).
[276] *Seelig, M. S., Berger, A. R.:* New Engl. J. Med. **290**: 974—975 (1974).
[277] *Seelig, M. S., Berger, A. R., Spielholz, N.:* Dis. Nerv. Syst. **36**: 461—465 (1975).
[278] *Seelig, M. S., Haddy, F. J.:* In: *Cantin, M., Seelig, M. S.* (eds.). Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, NY, 605—638 (1980). Proc. 2nd Int'l Mg. Sympos., 1976, Montreal, Canada.
[279] *Seelig, M. S., Heggtveit, H. A.:* Am. J. Clin. Nutr. **27**: 59—79 (1974).
[280] *Seelig, M. S., Vitale, J. J.:* In: *Durlach, J.* (ed.) Proc. 1st Intl. Mg. Sympos., 1971, Vittel, France, p. 515—522 (1973).
[281] *Selye, H.:* Acta Endocr. **28**: 273—278 (1958).
[282] —: Am. Heart J. **55**: 805—809 (1958).
[283] —: The Chemical Prevention of Cardiac Necroses. The Ronald Press Co., New York (1958).
[284] —: The Pluricausal Cardiomyopathies, Charles C. Thomas, Springfield, Illinois (1961).
[285] *Shukers, C. F., Knott, E. M., Schultz, F. W.:* J. Nutr. **22**: 53—64 (1941).
[286] *Silver, B. B., Seelig, M. S.:* (this Symposium).
[287] *Slater, J. E.:* Brit. J. Nutr. **15**: 83—97 (1961).
[288] *Slavin, J. L., Marlett, J. A.:* Am. J. Clin. Nutr. **33**: 1932—1939 (1980).
[289] *Sos, J.:* In: *Bajusz, E.* (ed.) Electrolyte and Cardiovasculars Diseases, S. Karger, Basel/New York; Williams & Wilkins, Baltimore, p. 161—180 (1965).
[290] *Spencer, H., Lesniak, M., Kramer, L., Osis, D.:* In: *Cantin, M., Seelig, M. S.,* (eds.) Magnesium in Health and Disease, SP Medical & Scientific Books, Jamaica, New York, p. 911—919 (1980). Proc. 2nd Int'l Mg Sympos., 1976, Montreal, Canada.
[291] *Spencer, I. O. B.:* Lancet **1**: 1288—1290 (1968).
[292] *Srivastava, U. S., Nadeau, M. J., Guennou, L.:* Nutr. Rep. Intl. **18**: 235—242 (1978).
[293] *Steiner, A. J.:* In: *Naito, H. K., Gerrity, R.* (eds.) *Nutrition and Cardiovascular Diseases.* SP Medical and Scientific Books, Jamaica, New York, (in press, 1981). Proc. 19th Ann. Mtg. of Am. Coll. of Nutr. Minneapolis, 1978.
[294] *Stephenson, M. G., Butler, L. C., Adams, Y. L.:* Fed. Proc. **29**: 696 (1970).
[295] *Stewart, A. K., Magee, A. C.:* J. Nutr. **82**: 287—295 (1964).
[296] *Stolley, P. D.:* Ann. Intern. Med. **76**: 661—663 (1972).
[297] *Stromme, J. H., Nesbakken, R., Normann, T., Skjortem, F., Skyberg, D., Johannessen, B.:* Acta Paediat. Scand. **58**: 433—444 (1969).
[298] *Sunderman, F. W.:* AM J. Clin. Path. **17**: 169—180 (1947).
[299] *Swanson, W. W.:* Am. J. Dis. Child. **43**: 10—18 (1932).
[300] *Szelenyi, I.:* In: *Durlach, J.* (ed.). Proc. 1st Int'l Mg. Sympos., Vittel, France, p. 195—211 (1971).
[301] —: World Rev. Nutr. Diet. **17**: 189—224 (1973).
[302] *Thoren, L.:* Acta Chir. Scand. (Suppl. 306): 1—65 (1963).
[303] *Tipton, I. H., Stewart, P. L.:* Dev. Appl. Spetroscopy **8**: 40—50 (1970).
[304] *Touitou, Y., Touitou, C., Bogdan, A., Beck, H., Reinberg, A.:* Clin. Chim. Acta **87**: 35—41 (1978).
[305] *Tower, D. B.:* Am. J. Clin. Nutr. 4: 329—344 (1954).
[306] *Turner, T. L., Cockburn, F., Forfar, J. O.:* Lancet 1: 283—284 (1977).
[307] *U.S. Dept. Agric. Nationwide Food Consumption Survey,* 1977—1978. Preliminary Report **$** 2. U.S.D.A. Sci. & Educ. Adm. (1980).
[308] *U. S. Senate Select. Comm. on Nutr. & Human Needs.* Dietary Goals for the U.S. U.S. Govt. Printing Office, Washington, D. C., 1978.
[309] *Unsigned.* New Engl. J. Med. **290**: 39—49 (1974).
[310] *Vallee, B. L. L.:* In: *The Enzymes,* in P. Boyer (ed.), Academic Press, N. Y., p. 225—270 (1960).
[311] *Varo, P.:* Int'l. J. Vitamin Nutr. Res. **44**: 267—273 (1974).
[312] *Vir, S. C., Love, A. H. G.:* Am. J. Clin. Nutr. **32**: 1934—1947 (1979).
[313] *Vitale, J. J., Hellerstein, E. E., Hegsted, D. M., Nakamura, M., Farbman, A.:* Am. J. Clin. Nutr. 7: 13—22 (1959).
[314] *Vitale, J. J., Velez, H., Guzman, C., Correa, P.:* Circ. Res. **12**: 642—650 (1963).
[315] *Vitale, J. J., White, P. L., Nakamura, M., Hegsted, D. M., Zamcheck, N., Hellerstein, E. E.:* J. Exp. Med. **106**: 757—766 (1957).
[316] *Wachstein, M., Graffeo, L. W.:* Obst. Gyn. **8**: 177—180 (1956).
[317] *Wachstein, M., Gudaitis, A.:* J. Lab. Clin. Med. **40**: 550—557 (1952).
[318] *Wacker, W. E. C.: Magnesium and Man.* Harvard Univ. Press., Cambridge, Mass. (1980).
[319] *Wacker, W. E. C., Iida, C., Fuji, K.:* Nature **202**: 659—662 (1964).
[320] *Wacker, W. E. C., Iida, C., Fuwa, K.:* Nature **206**: 90 (1965).
[321] *Wacker, W. E. C., Parisi, A. F.:* New Engl. J. of Med. **278**: 658—663, 712—717, 772—776 (1968).
[322] *Wacker, W. E. C., Vallee, N. L.:* New Engl. J. Med. **259**: 431—438, 475—482 (1958).
[323] *Walker, A. R. P., Fox, F. W., Irving, J. T.:* Biochem. J., **42**: 452—462 (1948).
[324] *Walker, M. A., Page, L.:* J. Am. Diet. Assoc. **70**: 260—266 (1977).
[325] *Wallach, S., Carter, A. C.:* Am. J. Physiol. **200**: 359—361 (1961).
[326] *Walser, M.:* Rev. Physiol., Biochem., Exp. Pharmacol. **59**: 185—296 (1967).
[327] *Wang, C. C. C., Kaucher, M., Wing, M.:* Am. J. Dis. Child. **52**: 41—53 (1936).
[328] *Wang, F. L., Wang, R., Khairallah, E. A., Schwartz, R.:* J. Nutr. **101**: 1201—1202 (1971).
[329] *Watchorn, E., McCance, R. A.:* Biochem. J. **26**: 54—64 (1932).
[330] *White, H. S.:* J. Am. Diet. Assoc. **55**: 38—43 (1969).
[331] *Widdowson, E. M.:* Lancet 2: 1099—1105 (1965).
[332] —: J. Roy. Coll. Phys. **3**: 285—298 (1969).
[333] *Widdowson, E. M., Dickerson, J. W. T.:* In Comar, C. L. & Bronner, F. (eds.). *Mineral Metabolism 2,* Academic Press, p. 2—247 (1961).
[334] *Widdowson, E. M., McCance, R. A., Spray, C. M.:* Clin. Sci. **10**: 113—125 (1951).
[335] *Wilkinson, A. W., Harris, I.:* Brit. J. Surg. **56**: 628 (1969).
[336] *Workshop on Magnesium Intervention Trials. WHO* Collaborating Centre for Ref. on Studies of Cardiovascular Disease in Relation to Water Quality. Ottawa, Canada, March 9—10 (1978).

[337] *Young, V. R., Scrimshaw, N. S.:* Am. J. Clin. Nutr. **32**: 486—500 (1979).
[338] *Zieve, L.:* Ann. N. Y. Acad. Sci. **162**: 732—743 (1969).
[339] —*:* Yale J. Biol. Med. **48**: 229—237 (1975).
[340] *Zieve, L., Doizaki, W. M., Stenroos, L. E.:* J. Lab. Clin. Med. **72**: 261—267, 268—277 (1968).
[341] *Zieve, F. J., Freude, K. A., Zieve, L.:* J. Nutr. **107**: 2178—2188 (1977).
[342] *Zuckerman, L., Marquardt, G. H.:* Proc. Soc. Exper. Biol. Med. **112**: 609—610 (1963).
[343] *Zuspan, E.:* J. Reprod. Med. **2**: 116—139 (1969).
[344] *Zuspan, F. P.:* Clin. Obst. Gyn. **9**: 954—972 (1966).
[345] *Zuspan, F. P., Pritchard, J. A., Quilligan, E. J.:* Contemp. Obst. Gyn. **6**: 12—15 (1975).