

Perspectives in Nutrition

The Requirement of Magnesium by the Normal Adult

Summary and Analysis of Published Data

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IT IS hoped that Perspectives in Nutrition will review the literature selectively, interpret it moderately and present a spectrum of ideas that will serve as a continual stimulation to nutritional research applied to medical problems.

MAGNESIUM has been accepted as an essential nutrient for the rat since 1932 when Kruse, Orent and McCollum¹ induced an acute magnesium deficiency syndrome in rats. The characteristics of magnesium deficiency were then studied in rats and in other laboratory animals by these investigators,²⁻⁶ and by Greenberg,⁷⁻¹⁰ Tufts et al.^{11,12} and Watchorn and McCance.¹³ In the past fifteen to twenty years, the early work on the magnesium deficiency syndrome has been verified and interrelationships of magnesium with other dietary factors have been elucidated. The systems affected in the acute deficiency state are primarily neuromuscular, cardiovascular and renal. Hyperirritability terminating in convulsions, hyperemia, vasodilation and trophic changes in the skin are initial manifestations of acute magnesium deficiency. Calcinosis of heart, muscle and kidney occur later.

During the 1930's and early in the war years, there was a flurry of interest in the possibility that magnesium depletion might play a role, in both man and farm animals, in conditions characterized by convulsions or by less severe manifestations of neuromuscular irritability. Haury and Hirschfelder¹⁴⁻¹⁸ correlated low plasma levels of magnesium with several clinical

conditions in which hyperirritability or convulsions are presenting signs, amongst which were epilepsy, eclampsia and renal insufficiency, as well as several pathologic states in which such signs are absent. Grass staggers of cattle, and the convulsions of calves fed only whole milk, were similarly found to be associated with low blood magnesium levels, and to be preventable by feeding magnesium supplements.¹⁹⁻²² Autopsy examination of the cows and calves that died in acute magnesium deficiency revealed severe cardiovascular damage, including necrosis and calcification.

Continuing biochemical investigations have established the importance of magnesium as a cofactor in enzymatic reactions of carbohydrate, protein and energy metabolism. Physiologic studies have demonstrated its participation in neuromuscular conduction, in protein synthesis and in maintenance of cellular integrity. There are several excellent review articles on the multiple roles of magnesium in the body economy.²³⁻³¹

Despite laboratory substantiation of the indispensability of magnesium, published articles indicating clinical interest in this cation were few until late in the 1950's. Martin and her co-workers, and McCollister and Flink and their colleagues, who have continued to contribute to the understanding of magnesium, then reported low plasma levels of magnesium

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in surgical patients receiving fluids parenterally,^{32,33} in patients receiving diuretic therapy^{34,35} and in diabetic patients.³⁶ They also correlated the signs and symptoms of acute alcoholism with magnesium depletion.³⁷⁻⁴¹ Recognition of magnesium deficit in additional pathologic clinical conditions, with or without overt, recognizable symptoms was soon provided by additional investigators.⁴²⁻⁴⁶ Neuromuscular and mental symptoms, ranging from tremor, nervousness and clouded sensorium through delirium, hallucinations and convulsions, were often most severe in patients with the lowest plasma magnesium levels, although the clinical findings could not always be correlated closely with the plasma levels of magnesium. In fact, it has been clearly demonstrated that patients with hypomagnesemia may be free of overt clinical symptoms of magnesium deficiency.^{44,47}

In the past few years, clinical interest in abnormal conditions associated with a deficit of magnesium has greatly increased. Metabolic balance studies,⁴⁸ measurement of cellular levels of magnesium⁴⁹⁻⁵² and use of tagged magnesium to measure exchangeable magnesium^{53,54} have all supported the contention that magnesium depletion can develop in several diseases. It is a risk, not only when magnesium losses are excessive (as in alcoholism, renal insufficiency, and in some patients on diuretics), but also when nutritional deficits develop as a consequence of disease. Recent work has substantiated the early finding of hypomagnesemia in postsurgical patients receiving magnesium-free fluids parenterally,^{55,56} in patients with malabsorption syndromes^{47,56-62} and in alcoholic patients with mixed nutritional deficits.^{56,63,64} Neuromuscular conditions associated with parathyroid disease have also been found, in both in the 1930's⁶⁵⁻⁶⁷ and more recent years, in association with abnormalities in magnesium metabolism.⁶⁸⁻⁷⁶ Recently a syndrome termed human magnesium-deficiency tetany, or spasmophilia, unassociated with parathyroid disease, has been described by Vallee et al.,^{30,56} Durlach et al.⁷⁷⁻⁷⁹ and by Rosselle and de Doncker.^{80,81}

Several additional groups of investigators have made important contributions to the

understanding of physiologic and pathologic factors influencing magnesium metabolism in man and have documented additional manifestations of the clinical deficiency syndrome.^{23,43,47,49,50,82-90} For example, Hanna and MacIntyre^{85,87} have described mental depression and muscle weakness with changes in electroencephalograms and electrocardiograms. By means of nutritional balance studies, tissue biopsies and determinations of exchangeable magnesium, they found that cellular magnesium levels may be significantly below normal despite essentially normal plasma levels, and that the bone magnesium in adult man is largely unavailable to make up a deficit in soft tissue magnesium.^{47,49} Smith and Hammarsten and their colleagues have shown erythrocyte levels of magnesium to be a more reliable index of hypermagnesemia or hypomagnesemia than plasma levels,⁵⁰ and like Barker,⁸³ McCollister⁸⁵ et al. have studied agents which influence the renal excretion of magnesium.^{88,90} An increasing number of clinical papers and editorials has appeared on the different aspects of the role of magnesium insufficiency in disease.^{27,59,64,91-104}

It is generally assumed that because magnesium is so plentiful in the typical diet, magnesium deficiency cannot develop in the absence of disease. This report presents an analysis of the published data on magnesium balance in normal men and women in different parts of the world. Contrary to the consensus, the customary diet in Occidental countries cannot be relied upon to provide sufficient magnesium to maintain equilibrium. Magnesium requirements should be reconsidered in the light of findings that indicate the likely development of negative balance on magnesium intakes below 6 mg. per kg. per day. Additional work should be carried out to ascertain, with more certainty, the optimal daily intake of magnesium. The acute deficiency syndrome probably develops only when pathologic conditions are superimposed on dietary inadequacy, a combination more frequent than has heretofore been recognized. A prolonged dietary insufficiency of magnesium may contribute to the development of chronic disease.

SOURCES AND COMPARISONS OF DATA

Data used herein have been collected from all reports in the literature that could be found on magnesium metabolic balance studies in normal healthy adults. The investigators and their geographic locations are indicated in the first columns of Tables I and II. The data were tabulated after converting the numerical values to a common base. Magnesium intake has been presented as milligrams of magnesium per kilogram of body weight per day* when the weights of the subject were given by the investigator; when body weights were not given, an average weight was assumed. The data from which balance determinations were calculated by the original investigators have been converted from milligrams excreted in urine or feces, to per cent of daily intake excreted in urine and feces.

Studies in which there was a rapid alteration of dietary intake, with the subjects on each diet for only a few days, have been excluded from Tables I and II except for the first control period during which the subjects were maintained on their customary or normal diet. Calculations of balances during less than a week are likely to result in error as the excretory levels may well reflect the intake of the previous period. Only those studies from which milligram per kilogram intakes could be derived have been included in Figures 1 through 5, which depict factors affecting magnesium balance. Studies giving only an average figure for several balance periods have been considered as one period, the value being weighted by multiplying the average by the number of days in the study.

As in all biological studies, individual differences being the rule rather than the exception,¹²¹ it is not surprising that the recorded values vary. The range of values of a group on one dosage regimen frequently overlaps the range of another. The accumulated averages at the different dosage levels, however, do in-

dicating a trend. To minimize individual discrepancies, and because the data obtained in long-term studies are more valid than those in short-term studies, the average balances and the percentages of intake excreted have been weighted by multiplying the figures by the number of days in each study. The data were too heterogeneous to justify calculation of statistical significance.

FACTORS IN ESTABLISHING DAILY REQUIREMENTS

The daily nutritional requirement for adults is established by determining the amount ingested which equals the total daily output. Because this is influenced by many variables, among which are the nutritional background of the subjects studied and the duration of the test diet, data obtained in short-term studies are less reliable than those in long-term studies. Evidence is presented that sweat losses should be considered in calculating magnesium requirements.

Measurement of Equilibrium

In establishing the daily requirements of a nutrient, it is necessary to ascertain the amount that must be ingested to make up for that lost in feces, urine, sweat and skin. The healthy adult subsisting on an adequate diet should be in equilibrium. Children, pregnant women and convalescent patients, in whom new tissue is being formed, require such additional amounts as will assure a positive balance. Many factors can contribute to a negative balance: inadequate dietary intake, faulty absorption or utilization and excess catabolism caused by pathologic processes. Even emotional disturbances have been shown to interfere with utilization of nutrients and to induce a negative balance.^{121,122}

As already stated the duration of the test diet will influence the validity of the results. Hathaway,¹⁰⁸ who recently made a detailed compilation of magnesium balance studies in man, has emphasized the fact that there is usually a lag of five days or more before the body can adjust to changes in nutrient intake. However, in children who had been maintained on a borderline intake (of calcium) subsistence on a good diet for as long as six months was

* To convert milligrams per day to milliequivalents per day, divide the magnesium entries by the conversion factor of 12, and the calcium figures by the conversion factor of 20.
$$\frac{(\text{mEq.} = \text{mg.} \times \text{valence})}{\text{At. weight}}$$

required before their retention was comparable to that of previously well fed children.¹²³ Thus, in determining nutritional requirements from metabolic balance data, it is preferable to rely on long-term studies. Hunscher,¹²¹ in her valuable discussion of factors to be considered in interpreting metabolic data, refers to the value of long-term studies in revealing changes in metabolic balances which develop as pre-existing deficits are corrected. For example, after being kept on an adequate calcium intake for over a year, calcium storage in a child declined from 541 mg. daily at the beginning of the study to 152 mg. daily.¹²⁴ Additional evidence is cited, from both laboratory and clinical sources, that a low nutritive status can cause a greater than expected retention. Hunscher also points out that tissue depletion may develop as a result of the gradual daily loss of relatively small amounts of the nutrient in question over a long period of time due to a dietary inadequacy. If abnormal circumstances supervene, which cause greater losses, an acute deficiency might develop in a much shorter period of time. It is pointed out that based on daily balance determinations in short-term balance studies a subject may appear to be in approximate equilibrium when he is in actual debt. In such a subject the nutrient, which had heretofore been supplied in insufficient amounts, would be stored when the diet was improved or supplemented.

It can be assumed that normal adults who go into positive balance when placed on a test diet, with or without supplementation, have been on a suboptimal intake; as a result a nutritional deficit develops which is indicated by the uptake of the nutrient as tissue stores are replenished. It has been reported¹²¹ that equilibrium of flow (of intake and output) can be attained at different tissue levels. Subjects with an inadequate nutritional background may reach equilibrium even on suboptimal intakes. Storage takes place when the intake is increased, after which a new balance is usually established. Even in apparently normal adults, in whom metabolic function is assumed to be adequate, use of the figures from balance studies must be regarded crit-

ically. Hunscher,¹²¹ has recently pointed out that such figures are valid only when the body content of the nutrient under study is sufficiently high for efficient metabolism. Thus, the nutritive background and the individual metabolic reactions influence the response to alterations in the diet. It may be assumed that once tissue needs are met, continued intake of optimal amounts will not be accompanied by retention, but by equilibrium, with the output equalling the intake.

Loss of Magnesium in Sweat

The magnesium balance in all studies recorded in Tables I, II and III was derived by subtracting the total renal and gastrointestinal magnesium excretions from the intake. No consideration was given to dermal losses. Although the amount of magnesium lost in sweat is small, it may tip the balance from equilibrium to negative, particularly in those on marginal intakes. Thus equilibrium should not be indicated by zero, at which intake is balanced by fecal and urinary excretion, but by a positive figure equal to the amount lost in sweat. This figure is variable in practice because electrolyte losses in sweat vary with the individual, the environmental temperature and physical activity.

The first investigators to observe that neglect of losses in the sweat may invalidate a metabolic experiment were Mitchell and Hamilton.¹²⁷ In 1949, they presented evidence that appreciable amounts of nitrogen and minerals are lost even under minimal sweating conditions. Unfortunately, their studies of magnesium sweat loss were carried out only under conditions of heat. Sweat was collected from men exposed to controlled environments in an air-conditioned chamber for five and a half days a week (7.5 hours a day). They found that under hot, humid conditions, the initial output of magnesium and calcium was relatively high but it soon declined. Magnesium losses averaged 0.22 mg. per cent in the first samples, and 0.06 mg. per cent in the last samples. Calcium values averaged ten times as much in the first samples, and somewhat more than ten times as much in the last samples. Other studies showed the magnesium content of sweat to

range between 0.1 and 19 mg. per cent, depending upon the conditions under which the studies were carried out.¹²⁸⁻¹³² Most of the determinations indicated the magnesium content of sweat to be somewhat under 1 mg. per cent. Most recently, Consolazio et al.,¹³³ on the basis of a study of three healthy young men kept at temperatures of 100°F. and 70 per cent humidity during four four-day periods of 7.5 hours each, reported that sweat losses of magnesium were fairly stable (0.7 to 0.6 mg. per cent) and apparently did not change much with time. This group found the total daily sweat losses of magnesium under these conditions to be from 15.2 to 17.8 mg. per cent; these figures pertain only to the total loss during the 7.5 hour test period. In three overnight exposures to temperatures of 100°F., an average of an additional 29.7 mg. per cent was lost. It may be noted that these three young men exhibited a strongly positive magnesium balance (about 200 mg. per day) during the study on a daily intake of 343 mg. of magnesium and a relatively low calcium intake (581 mg. per day).¹³⁴ The very low urinary and fecal excretion of magnesium (7 to 8 per cent of the daily intake in the urine, and 33 per cent of the intake in the feces) suggests that there is some renal and intestinal conservation of magnesium during acute periods of excessive perspiration. (See Figure 3, columns which give the data for magnesium intakes of 4 to 5.9 mg. per kg. per day for comparative values.)

No data are available on magnesium losses by healthy adults under comfortable environmental conditions. If the magnesium content of the insensible sweat bears the same relationship to the content of calcium as it does under conditions of thermal stimulation, the daily sweat loss of magnesium should be about a tenth of the value for calcium. Data on sweat losses of calcium under normal conditions have been provided by Mitchell and Hamilton,¹²⁷ who reported that calcium losses under comfortable conditions average 149 mg. per day. The more recent study by Consolazio et al.¹³³ performed on healthy young men at low and adequate calcium intakes under temperate conditions, shows the loss of calcium in the sweat to be somewhat greater at the lower intake than at

the higher intake level, 194 and 155 mg., respectively. Using the Consolazio data for the higher calcium intake,¹³³ which corresponds more closely to the typical American calcium intake, and the Mitchell observations¹²⁷ as reference data, it seems likely that the magnesium sweat loss under temperate conditions may be at least 15 mg. a day. This figure does not allow for increased losses under conditions of undue heat, when sweating is more profuse, as in the tropics or during the summer months.

The conservative estimate of a dermal loss of 15 mg. of magnesium daily is indicated in Figures 1, 2, 3 and 5, by a shaded area between 0 and +15, and by the two entry lines for percentage of negative balance periods at 0 and +15 in Figures 1 and 3. In all likelihood, balances below +15 mg. per day are actually negative. In the case of calcium (Fig. 4) the percentages of negative balance periods at an equilibrium of 0, +100 and +150, are entered separately to indicate the probable calcium equilibrium, taking possible sweat losses into account.

STUDIES OF MAGNESIUM BALANCE

Magnesium balance determinations, collected from the literature, are presented in summary form in Tables I (men) and II (women). These tables permit comparisons of average daily and cumulative balances, and of percentages of intake excreted, at different levels of intake. The balance periods are grouped according to the following three categories of magnesium intake: (1) below 5 mg. per kg. per day, which was inadequate to maintain equilibrium in most of the balance periods; (2) between 5 and 10 mg. per kg. per day, which is the range in which minimal to optimal daily requirements are probably met; (3) above 10 mg. per kg. per day, which is probably a high intake, needed only if severe deficits must be met.

The data presented in detail in Tables I and II are combined and analyzed in Figure 1. There is evidence that women can maintain equilibrium on a lower magnesium intake than men.

Low Magnesium Intake

On the basis of 105 balance periods in men and 146 in women, totaling 658 and 781 days,

respectively, it appears that negative balances are likely to develop in either sex on magnesium intakes under 4 mg. per kg. per day. At this level, the average daily balances were below 0 (the point at which the dietary intake equals that excreted in stool and urine) for both men and women. The negative balance was greater for men than for women (average daily loss was -37 mg. in men, and -3 mg. in women), and the balance periods which were negative at 0 are 75 per cent of the total for men and 63 per cent for women. With an allowance of 15 mg. daily for minimal or obligatory sweat loss, negative periods were recorded in 83 per cent of the studies on men, and in 73 per cent of those on women. Of interest is the apparently greater fecal excretion of magnesium at the same low daily intake by men (81 per cent of intake) as compared with women (58 per cent), and with both men and women at the higher intakes (58 to 62 per cent).

At 4 to 4.9 mg. per kg. per day, based on 861 test days for men and 1,082 test days for women, the average daily loss of magnesium was somewhat less. In terms of percentages of balance periods which were negative or positive, negative magnesium balances were somewhat more frequent than positive balances at the point at which intake was equal to urinary and fecal output. If 15 mg. is allowed for sweat loss, 72 per cent of the balance periods for men were negative. The women, however, showed the same percentage balance distribution at both 0 and +15 (56 and 55 per cent). The over-all average daily balance at the 4 to 4.9 mg. per kg. intake showed a loss of 13 mg. in men, not considering sweat losses, and a positive balance of 13 mg. in women, which may be barely sufficient to maintain equilibrium under conditions of low activity and minimal sweat loss.

That the cumulative losses in men at a magnesium intake below 5 mg. per kg. may be large, is indicated both by the data in Figure 2, which presents the results of an analysis of only the long-term studies, and by the cumulative balance column in Table I. The longest study was reported in 1926 by Clark,¹⁰⁵ who performed extensive metabolic studies with five San Quentin prisoners. One (Case 1)

lost over 2 gm. of magnesium during sixteen weeks on a magnesium intake of 3.7 to 4.1 mg. per kg.; one (Case 2) lost 5.5 gm. on an intake below 4 mg. per kg. for sixteen weeks; one (Case 3) lost 3.5 gm. in sixteen weeks on an intake below 4 mg. per kg. and continued to lose 2.25 gm. more during an eight week period on 5.6 mg. per kg.; one (Case 4) lost a total of 7.8 gm. of magnesium during nineteen weeks on an intake below 4 mg. per kg., at which time he was withdrawn from the study; and one (Case 5) lost a total of 9.5 gm. of magnesium during the entire twenty-eight week period of study, including a two week period of magnesium supplementation. This last subject, however, gave a history of renal disease before entering prison, and may not have been normal at the time of the study. Magnesium losses as high as 1.5 to 3.5 gm. over a fifty day test period were also reported more recently by Irwin, in the Hathaway report¹⁰⁸ for male students (Cases 20, 22 and 24) on magnesium intakes below 5 mg. per kg. per day. Two additional students (Cases 19 and 30) showed losses of over 1.5 and 1 gm. during the fifty days on an intake of 5.2 and 5.5 mg. per kg. per day. Figure 2 shows that although the women were apparently able to conserve magnesium during long periods of low magnesium intake, as indicated by the change in magnesium balance at an intake below 4 mg. per kg. per day from +2 during the first period to +17 for the last, men did not appear to have this capacity. Starting at -36 mg., the average daily balance was -24 mg. at the end of the studies. At the 4 to 4.9 mg. per kg. per day intake, a slight improvement in retention by men was apparent, to +13, from -15. This balance may be just adequate to maintain equilibrium under conditions of minimal sweat loss, but would be insufficient to make up for the tissue losses suffered earlier. The studies with women at the 4 to 4.9 mg. per kg. daily intake showed little change in balance: +13 to +15 (the over-all balance figure) and +6 (entry for the last test period). There are no data for women kept on magnesium-deficient diets for as long as the men in the early Clark studies. The studies by Leverton and Linkswiler¹⁰⁸ with young women students show, however, that cumulative losses

to 641 mg. (5.7 to 11.5 mg. per kg. per day). Basu and Malakar,¹¹² in their study of Indian men on diets to which they had been accustomed, concluded that the daily magnesium intake fell between 6.1 and 10.6 mg. per kg. (Cases 46 and 47). Chu et al.,¹¹⁵ in their 1941 study of calcium, phosphorus and magnesium metabolism in healthy young Chinese men and women from the upper classes, reported that the magnesium intake on self-selected diets, before the experimental alterations of the diets, ranged from 6.5 to 10.6 mg. per kg. per day (Cases 54-59, Table I; Cases 126-131, Table II).

Detection of Magnesium Deficiency

The foregoing data indicate that magnesium deficiency is common in the Western countries. The failure to identify slight to marked clinical deficiency of magnesium is understandable since the tissues affected by the acute deficiency of magnesium are those of the cardiovascular, renal and neuromuscular systems. In none of these tissues are early changes easy to detect. In addition, in mild to moderate deficiency states plasma levels of magnesium are likely to be unchanged.

In the acute depletion study, reported by Fitzgerald and Fourman,⁸⁴ despite losses of 550 and 860 mg. of magnesium over a twenty- to twenty-four-day observation period, there was no change in plasma levels, and no abnormal symptoms, except that both subjects reported feeling weaker during the periods of depletion than during the control periods. The same investigators have recently reported finding entirely unexpected large deficits of magnesium in patients with a history of malabsorption, but without symptoms of magnesium deficiency.⁶¹ The three patients whose studies were completed showed a cumulative retention of magnesium of 440 to 460 mEq. (5.3 to 5.5 gm.) over the forty to eighty days during which they received oral and parenteral supplements of magnesium. Two patients felt a considerable gain of muscular strength when the unsuspected magnesium deficit was corrected. Like the patient described by Petersen,¹⁵⁴ one also had a persistently low plasma calcium level which rose on correction of the

magnesium deficit, and showed improvement of previously intractable tetany.

Even when symptoms of magnesium deficiency are detectable, plasma magnesium levels may remain within normal limits.^{50,51,102} In rats on acute magnesium-deficient diets Tufts and Greenberg¹¹ showed that there was an initial drop in the plasma magnesium level which swung back to nearly normal after three days to two weeks, despite the development of convulsions of deficiency. The erythrocyte level, on the other hand, which dropped somewhat more slowly than the plasma level, reached and remained at levels approximately half normal. Clinical studies in patients with magnesium deficiency secondary to alcoholism, reported by Smith et al.,^{50,51} showed a slight average decrease in plasma magnesium in twelve patients, two of whom had values within normal limits. The erythrocyte values, however, showed a 40 per cent decrease in the mean, as compared with normal levels. MacIntyre et al.⁴⁹ have reported a marked degree of magnesium depletion in patients with malabsorption, which was detected by muscle biopsy analysis. Two patients, who also had renal impairment, had plasma magnesium levels within normal limits.

Thus, it is apparent that subacute or chronic magnesium inadequacy is difficult to detect. Since even acute deficiency states are not always accompanied by significant changes in plasma levels of magnesium, it is unlikely that measurement of plasma levels will be useful for diagnosis of clinical magnesium deficiency. Magnesium being primarily an intracellular cation, possibly erythrocyte levels will provide more reliable data; probably muscle biopsy would be of greater value.

COMMENTS

Published metabolic data show that the daily intake of magnesium from the typical American and British dietary is insufficient to maintain equilibrium. However, it is widely assumed by clinical investigators who are actively engaged in elucidating both the nature and characteristics of the magnesium deficiency syndrome in disease states, and the

mechanisms by which acute magnesium depletion is brought about, that magnesium is so ubiquitous in the diet that it is virtually impossible to develop a deficiency under normal conditions. The premise that the magnesium intake is more than adequate for maintenance of health on any normal diet, and that magnesium deficiency can develop only under distinctly pathologic conditions has been averred repeatedly.^{23,29,37,48,53,61,91,98,108,171,175}

Contributing to the belief that most diets contain enough magnesium for the normal subject, is the general acceptance of no more than 300 mg. of magnesium as the daily requirement, an amount which is supplied by the average American diet. However, the wide range of published opinions as to the optimal or minimal magnesium requirements bespeaks confusion in this area of nutrition. As little as 10 to 12 mg. per day has been cited as being sufficient,^{135,175} and an intake as high as 600 mg. per day has been advised.¹⁰ Clearly not all these recommendations can be valid. The statement that 10 mg. per day meets requirements for growth arose as a misquotation of an article by Duckworth and Warnock,¹⁷¹ who actually gave the requirements during growth as 11 to 15 mg. per kg. per day, and the adult requirement as 250 mg. per day for men and 220 mg. per day for women (400 mg. during pregnancy). The 12 mg. per day minimal requirement was derived from the obligatory loss during a depletion study in women,¹³⁵ which is not the accepted means of ascertaining nutritional requirements.

The established method for determining normal nutritional requirements of the adult is based on ascertaining the amount of the nutrient which must be ingested to meet the normal daily output. Unfortunately, the two early publications on magnesium balance, which led to wide acceptance of 220 to 300 mg. of magnesium as the daily requirement, dealt with short-term studies.^{106,111} Analysis of both papers, presented earlier in this report, reveals that neither is indicative of maintenance of equilibrium under dietary conditions corresponding to those of the usual American diet. Furthermore, short-

term studies are difficult to interpret. The extent of tissue saturation or deficiency influences the amount of nutrient retained, and adjustment to alterations of dietary intake with equilibration at the new level, may take longer than the few days of observation in the short-term studies cited. Of all the papers on magnesium nutrition, only one recommended as much as is shown to be necessary in this report. Greenberg and his co-workers,¹⁰ who did much of the pioneer work with magnesium deficiency in rats, published a review article in 1935 in which they stated that an adult man requires 600 mg. per day of magnesium. In the most recent compilation of metabolic balance data, Hathaway¹⁰⁸ gave the average daily requirement of magnesium as 300 mg. for women and 300 to 400 mg. for men.

In establishing a nutritional requirement, the amount designated should be sufficient to maintain equilibrium in all subjects. When the nutritional requirement is derived from analysis of the response of many subjects with different nutritional backgrounds to different intakes, the amount which allows for equilibrium on the average should not be selected as the optimal intake. Such an amount will meet the needs only of the portion of the population that can be kept in balance at that intake, or less. Those who require more to maintain equilibrium will be in negative balance. Thus, in deriving the requirement from the data analyzed in this report, the intake was selected at which equilibrium or positive balance was reached in at least three fourths of the subjects. On this basis, the minimal daily requirement is 6 mg. per kg. per day. For a 140 pound woman, this comes to 385 mg. of magnesium daily; for a 185 pound man, at least 500 mg.

It is questionable, however, whether even this much magnesium can be relied upon to maintain equilibrium consistently, in the face of the many factors which have been shown to interfere with either the absorption or retention of magnesium. For example, several dietary constituents have been shown to interfere with the retention, or to increase the requirement, of magnesium, particularly when its supply in the diet is inadequate. Three such nutrients in which the American

diet is rich are calcium, protein and vitamin D. Another "dietary factor" often ingested in Western countries, which causes magnesium loss, is alcohol. Chronic alcoholism was one of the first conditions associated with magnesium deficiency. It is true that chronic malnutrition may well play a role in such cases. Studies of administration of alcohol in varying quantities to normal subjects, however, reveal that alcohol itself causes marked magnesium diuresis,^{88, 35, 176} and that the degree of urinary loss is greater in subjects with pre-existing magnesium deficiency than in those with a history of normal nutrition.⁸⁸

Therefore, it appears that an intake of 7 to 10 mg. per kg. per day is preferable to 6 mg. per kg. per day for subjects whose dietary preferences include foods rich in protein and calcium, and are supplemented with vitamin D. Such an intake will also allow for increased magnesium excretion caused by physiologic factors, pharmacologic agents or even social drinking. On this basis, a 185 pound man would require as much as 580 to 800 mg. per day of magnesium, probably approximately twice as much as his diet normally delivers. Possibly, the requirements for women are somewhat less. It is noteworthy that most of the subjects described in the Oriental studies were provided with 7 to 10 mg. per kg. per day of magnesium on their customary diets.

If such a large intake of magnesium is, indeed, required, and if cumulative deficiencies develop on the typical Western diet which usually contains no more than 5 mg. per kg. per day and not infrequently as little as 4 mg. per kg. per day, why is magnesium deficiency not more frequently recognized? A clue to the clinical silence of subacute magnesium deficiency has been provided by the acute depletion study reported by Fitzgerald and Fourman.⁸⁴ Despite cumulative losses of 550 to over 800 mg. during the twenty to twenty-four-day observation periods, no change in plasma levels of magnesium, or adverse symptoms, other than some muscular weakness, developed. Early changes in the other tissues known to be affected by acute deprivation of magnesium in animals, such as those

of the cardiovascular, renal and neurologic systems, escape observation. Using an epidemiologic approach, however, an interesting correlation can be observed. Men of the Western countries, who are known to be more subject to cardiovascular disease than women or inhabitants of the Oriental countries, stand out as those most likely to have negative magnesium balance. From the data presented in this paper, it seems that men require more magnesium than women to remain in equilibrium, and that they lose more magnesium than women on magnesium-poor diets. In the Orient, the dietary supply of magnesium appears to be sufficient to meet daily needs; whereas in the Occident, the daily supply is marginal or definitely insufficient, especially for men. Thus, it is possible that arteriosclerosis may be, in part, a disease of malnutrition.

Analysis of published metabolic studies having led to some provocative findings, definitive nutritional investigations are indicated. Metabolic balance studies should be designed so as to determine whether a deficit of magnesium exists at the outset of the study. The diet should be supplemented with magnesium until equilibrium is established. The amount of magnesium stored during the period of supplementation should be noted, and the amount of magnesium required daily to maintain balance should then be determined. Once tissue needs are met, continued administration of the amount of magnesium which previously resulted in positive balance can be expected to result in excretion of the excess, resulting in establishment of equilibrium.

The apparent tendency of women to lose less magnesium than men, and to maintain equilibrium while on low magnesium intakes, should be explored by means of controlled studies of men and women under the same conditions. Studies of the difference in magnesium balance on low and supplemented magnesium diets, according to age, should also be undertaken. The studies analyzed in this paper were all carried out in healthy young adults.

Evaluation of the benefit which may accrue

from providing an optimal intake of magnesium will unquestionably be difficult. Magnesium being an intracellular cation, tissue levels will provide a more reliable index of response to magnesium administration than plasma levels. Since subacute or chronic deficiency is apparently symptom-free, unless the weakness reported in subjects whose intake or retention of magnesium was poor can be considered symptomatic of deficiency, clinical improvement on magnesium supplementation will be difficult to evaluate. As regards pathologic findings which may develop before overt symptoms are detected, they are likely to be in the tissues in which severe damage is seen in experimental animals depleted of magnesium. Since these tissues cannot readily be subjected to scrutiny, early damage is difficult to detect. It is suggested that chronic magnesium inadequacy may participate in the pathogenesis of chronic diseases of the cardiovascular system, and in the more acute conditions characterized by tetany or convulsions, in which magnesium loss has already been implicated. It is tempting to speculate that the lower incidence of arteriosclerosis in the East and among Western women as compared with Western men may be related, in part, to the higher magnesium content of Eastern diets and the greater capacity of women than men to retain magnesium. Additional evidence of the role of magnesium in cardiovascular function and disease will be presented in a second report.

SUMMARY

The widespread assumption that the average daily intake of magnesium is sufficient to maintain equilibrium in the normal adult has been questioned. Analysis of published metabolic data indicates that the minimal daily requirement is not 220 to 300 mg. per day, as has been reiterated, or even 5 mg. per kg. per day as has also been suggested, but probably at least 6 mg. per kg. per day.

The available clinical metabolic data provide evidence that at intakes below 6 mg. per kg. per day, negative magnesium balance is likely to develop, particularly in men. Women seem to retain more magnesium than men at

low and marginal magnesium intakes. At intakes above 10 mg. per kg. per day, strong positive magnesium balances develop, which probably reflect repletion of suboptimal tissue stores. High protein, calcium and vitamin D intakes, and alcohol all function to impede retention or to increase the requirement of magnesium, particularly in those on low magnesium intakes. On magnesium intakes above 6 mg. per kg. per day, little interference with magnesium retention by calcium, protein or vitamin D has been reported.

The diet in the Orient apparently provides 6 to 10 mg. per kg. per day. The Occidental diet, however, provides an average of 250 to 300 mg. of magnesium daily, or less than 5 mg. per kg. per day for most adults. Because the Western diet is often also rich in protein, calcium and vitamin D, and alcohol ingestion is common, it is suggested that the optimal daily intake of magnesium should be 7 to 10 mg. per kg. per day.

The existence of subacute or chronic magnesium deficiency is difficult to diagnose. Because the tissues damaged by magnesium depletion are those of the cardiovascular, renal and the neuromuscular systems, early damage is not readily detectable. It is postulated that long-term suboptimal intakes of magnesium may participate in the pathogenesis of chronic diseases of these systems.

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